FORMULATION DEVELOPMENT AND EVALUATION OF CANDESARTAN CILEXETIL IMMEDIATE RELEASE TABLETS

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PERIYANAHALLI-635205,

DHARMAPURI,TAMILNADU.

CERTIFICATE

This is to certify that the dissertation entitled

"FORMULATION DEVELOPMENT AND EVALUATION OF CANDESARTAN CILEXETIL IMMEDIATE RELEASE TABLETS"

Constitutes the original work carried out by

(Reg. No-26106808)

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Satish Chilakapati

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EVALUATION CERTIFICATE

This is to certify that this dissertation entitled **"Formulation Development and Evaluation of Candesartan Cilexetil immediate release Tablets"** constitutes the original work carried out by **Mr.Satish Chilakapati B.Pharm.,** under the guidance and supervision of **Dr.R.P.Ezhilmuthu, M.Pharm., Ph.D., Head of Department**, Department of Pharmaceutics, Padmavathi College of Pharmacy & Research Institute, Periyanahalli, Dharmapuri - 635205 has been evaluated on _____.

Evaluators:

1. **2.**

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LIST OF ABBREVIATIONS

S.NO	Symbols	Abbreviation
1	%	Percentage
2	BP	British Pharmacopoeia
3	mmHg	Millimetre of Mercury
4	<	Less than
5	>	Greater than
6	ACE	Angiotensin converting enzyme
7	ARB	Angiotensin II Receptor Blockers
8	AT1	Angiotensin 1
9	DDS	Drug delivery system
10	IR	Immediate release
11	CR	Controlled release
12	GI	Gastro intestinal
13	UV	Ultra violet
14	CMC	Carboxy methyl cellulose
15	HPMC	Hydroxyl propyl methyl cellulose
16	USP	United states pharmacopoeia
17	PVP	Polyvinyl Pyrolidine
18	PEG	Polyethylene Glycol
19	SLS	Sodium Lauryl sulfate
20	MLS	Magnesium lauryl sulfate
21	w/w	Weight by weight
22	CHF	Congestive heart failure
23	DSC	Differential scanning colorimetry
24	CSM	Cavernous smooth muscle
25	Vd	Volume of distribution
26	API	Activep pharmaceutical ingredient

27	HCTZ	Hydrochlorthiazide
28	HPC	Hydroxy propyl cellulose

1.INTRODUCTION

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience in administration, and cost-effective manufacturing process. For many drug substances, conventional immediate-release formulations provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamic profiles with an acceptable level of safety to the patient. ***.(A Gupta et.al.,2010)***

Based on the desired therapeutic objectives, oral DDS may be assorted into three categories:

- Immediate-release preparations,
- Controlled-release preparations and
- Targeted- release preparations.

Immediate-Releasae Prepartions

These preparations are primarily intended to achieve faster onset of action for drugs such as analgesics, antipyretics, and coronary vasodilators. Other advantages include enhanced oral bioavailability through transmucosal delivery and pregastric absorption, convenience in drug administration to dysphasic patients, especially the elderly and bedridden, and new business opportunities.

Conventional IR formulations include fast disintegrating tablets and granules that use effervescent mixtures, such as sodium carbonate (or sodium bicarbonate) and citric acid (or tartaric acid), and superdisintegrants, such as sodium starch glycolate, crosscarmellose sodium, and crospovidone. Current technologies in fast-dispersing dosage forms include modified tableting systems, floss or Shear form technology, which employs application of centrifugal force and controlled temperature, and freeze-drying. ***(Y.H. Lee et.al, 2000)***

Advantages of Immediate Release Drug Delivery System

An immediate release pharmaceutical preparation offers:

1. Improved compliance/added convenience
2. Improved stability
3. Suitable for controlled/sustained release actives
4. Allows high drug loading.
5. Ability to provide advantages of liquid medication in the form of solid preparation.
6. Adaptable to existing processing and packaging machinery
7. Cost- effective***(Reddy.L.H et al.,2002)***

Desired Criteria for Immediate Release Drug Delivery System

An immediate release dosage form should dissolve or disintegrate in the stomach within a short period.

1. In the case of liquid dosage form it should be compatible with taste masking.
2. Be portable without fragility concern.
3. Have a pleasing mouth feel.
4. It should not leave minimal or no residue in the mouth after oral administration.
5. Exhibit low sensivity to environmental condition as humidity and temperature.
6. Be manufactured using conventional processing and packaging equipment at low cost.
7. Rapid dissolution and absorption of drug, which may produce rapid onset of action.

(A Gupta et.al.,2010)

EXCIPIENTS

Excipients balance the properties of the actives in Immediate release dosage forms. This demands a thorough understanding of the chemistry of these excipients to prevent interaction with the actives. Determining the cost of these ingredients is another issue that needs to be addressed by formulators. The role of excipients is important in the formulation of fast-melting tablets. These inactive food-grade ingredients, when incorporated in the formulation, impart the desired organoleptic properties and product

efficacy. Excipients are general and can be used for a broad range of actives, except some actives that require masking agents.

BULKING MATERIALS

Bulking materials are significant in the formulation of fast-melting tablets. The material contributes functions of a diluent, filler and cost reducer. Bulking agents improve the textural characteristics that in turn enhance the disintegration in the mouth, besides; adding bulk also reduces the concentration of the active in the composition. The recommended bulking agents for this delivery system should be more sugar-based such as mannitol, polydextrose, lactitol, DCL (direct compressible lactose) and starch hydrolystate for higher aqueous solubility and good sensory perception. Mannitol in particular has high aqueous solubility and good sensory perception. Bulking agents are added in the range of 10 percent to about 90 percent by weight of the final composition.

EMULSIFYING AGENTS:

Emulsifying agents are important excipients for formulating immediate release tablets they aid in rapid disintegration and drug release. In addition, incorporating emulsifying agents is useful in stabilizing the immiscible blends and enhancing bioavailability. A wide range of emulsifiers is recommended for fast-tablet formulation, including alkyl sulfates, propylene glycol esters, lecithin, sucrose esters and others. These agents can be incorporated in the range of 0.05 percent to about 15 percent by weight of the final composition.

LUBRICANTS

Lubricants, though not essential excipients, can further assist in making these tablets more palatable after they disintegrate in the mouth. Lubricants remove grittiness and assist in the drug transport mechanism from the mouth down into the stomach.

SUPER DISINTEGRANTS

A disintegrant is an excipient, which is added to a tablet or capsule blend to aid in the break up of the compacted mass when it is put into a fluid environment. ***.(A Gupta et.al.,2010)***

ADVANTAGES:

1. Effective in lower concentrations
2. Less effect on compressibility and flowability
3. More effective intragranularly

Some super disintegrants are

- **Sodium Starch Glycolate** used in concentration of 2-8 % & optimum is 4%.

Mechanism of Action Rapid and extensive swelling with minimal gelling. Microcrystalline cellulose (Synonym: Avicel, celex) used in concentration of 2-15% of tablet weight. And Water wicking.

- **Cross-linked Povidone (crospovidone) (Kollidone)** used in concentration of 2-5% of weight of tablet. Completely insoluble in water.

Mechanism of Action Water wicking, swelling and possibly some deformation recovery. Rapidly disperses and swells in water, but does not gel even after prolonged exposure. Greatest rate of swelling compared to other disintegrants. Greater surface area to volume ratio than other disintegrants.

- **Low-substituted Hydroxyl Propyl Cellulose,** which is insoluble in water. Rapidly swells in water. Grades LH-11 and LH-21 exhibit the greatest degree of swelling. Certain grades can also provide some binding properties while retaining disintegration capacity. Recommended concentration 1-5% .

- **Cross-linked Carboxy Methyl Cellulose Sodium (Croscarmellose Sodium**

Mechanism of Action Wicking due to fibrous structure, swelling with minimal gelling. Effective Concentrations: 1-3% Direct Compression, 2-4% Wet Granulation.

Gas Producing Disintegrants

Gas producing disintegrants are used especially where extra rapid disintegration or readily soluble formulation is required. They have also been found of value when poor disintegration characteristics have resisted other methods of improvement. Care should be taken during tab letting, particularly on moisture level. Composition is based upon the

same principles as those used for effervescent tablets, the most common being mixtures of citric & tartaric acids plus carbonates or bicarbonates.

In many instances lower concentration can be used with gas producing disintegrants than are required by other disintegrating agents. Certain peroxides that release oxygen have been tried, but they do not perform as well as those releasing carbon dioxide.

Controlled-Release Preparations

The currently employed CR technologies for oral drug delivery are diffusion-controlled systems; solvent activated systems, and chemically controlled systems. Diffusion-controlled systems include monolithic and reservoir devices in which diffusion of the drug is the rate-limiting step, respectively, through a polymer matrix or a polymeric membrane. Solvent-activated systems may be either osmotically controlled or controlled by polymer swelling. Chemically controlled systems release drugs via polymeric degradation (surface or bulk matrix erosion) or cleavage of drug from a polymer chain. It is worth mentioning here that the so-called programmed-release (‘‘tailored-release’’) profile of a final CR product is rarely the outcome of a single pharmaceutical principle. Depending on the specific physicochemical properties of the drug in question and desired therapeutic objectives, different formulation and CR principles may be proportionally combined within the same dosage form. This task appears to be simpler when realized in terms of appropriate selection of polymers and excipients that incorporate desired principles.***(S.J. Wu et.al,1999)***

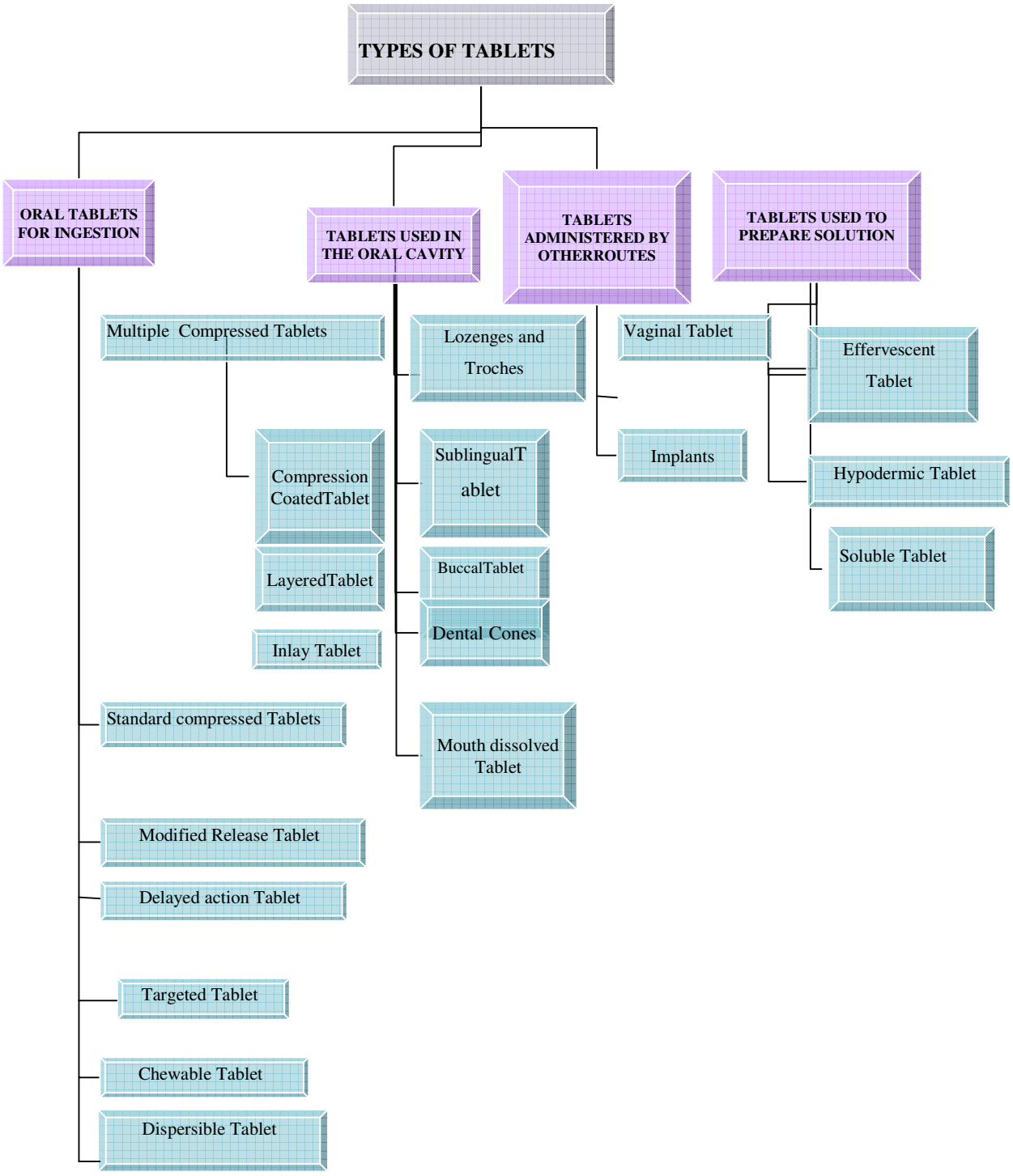
Targeted-Release Preparations

Site-specific oral drug delivery requires spatial placement of a drug delivery device at a desired site within the GI tract. Although it is virtually possible to localize a device within each part of GI tract, the attainment of site-specific delivery in the oral cavity and the rectum is relatively easier than in the stomach and the small and large intestines. The latter requires consideration of both longitudinal and transverse aspects of GI constraints. Some of the potential CR and site-specific DDSs will be described.***(Jennifer Sudimack et.al,2000)***

1.1 Types of Tablets

With advancement in technology and increase in awareness towards modification in standard tablet to achieve better acceptability as well as bioavailability, newer and more efficient tablet dosage forms are being developed.

FIGURE NO: 1 TYPES OF TABLETS



1.1.1 Oral tablets for Ingestion

These tablets are meant to be swallowed intact along with a sufficient quantity of potable water. Exception is chewable tablet. Over 90% of the tablets manufactured today are ingested orally. This shows that this class of formulation is the most popular worldwide and the major attention of the researcher is towards this direction. ***(Lachman L et.al,)***

1.1.1.1 Multiple Compressed Tablets

The tablets in this category are prepared for two reasons: to separate physically or chemically incompatible ingredients and to produce repeat action/ prolonged action tablet.

The tablet manufacturing machine is generally operated at relatively lower speed than for standard compression tablet. There are three categories under this class:

I. Multilayered tablets – two to three component systems.

II. Compression coated tablets – tablet within a tablet.

III. Inlay tablet – coat partially surrounding the core.

The layered tablet is preferred over compression coated tablet as the surface contact is less and the production is simple and more rapid.

I. Multilayered Tablets

When two or more active pharmaceutical ingredients are needed to be administered simultaneously and they are incompatible, the best option for the formulation pharmacist would be to formulate multilayered tablet. It consists of several different granulations that are compressed to form a single tablet composed of two or more layers and usually each layer is of different colour to produce a distinctive looking tablet. Each layer is fed from separate feed compression to avoid contamination. Therefore, each layer undergoes light compression as each component is laid down. This avoids granules intermixing if the machine vibrates. For example, admixture containing PhenylephedrinHCL and Ascorbic Acid with Paracetamol.

Paracetamol + phenylephedrine Hydrochloride → one layer

Paracetamol + ascorbic acid → another layer.

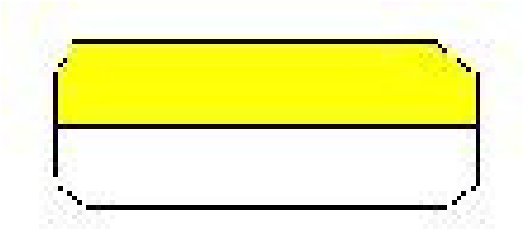


Figure No:2 Multilayered Tablet

II. Compression Coated Tablets

This type of tablet has two parts, internal core and surrounding coat. Thecore is small porous tablet and prepared on one turret. For preparing finaltablet, a biggerdie cavity in another turret is used in which first the coatmaterial is filled to half and then core tablet is mechanically transferred,again the remaining space is filled with coat material and finally compressionforce is applied. This tablet readily lend itself in to a repeat action tablet as the outer layer provides the initial dose while the inner core release the drug later on. But, when the core quickly releases the drug, entirely different blood level is achieved with the risk of over dose toxicity. To avoid immediate release of both the layers, the core tablet is coated with enteric polymer sothat it will not release the drug in stomach while, the first dose is addedin outer sugar coating. Even so, coating operation requires interpretation while manufacturing and dawdling the manufacturing process. Sometimes, inner coremay be of liquid formulation to provide immediate release of core after the coat gets dissolved. . (***Rawlins EA editor, 1995).***

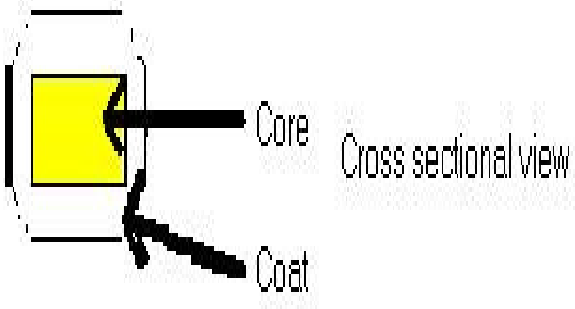


Figure No:3 Compression Coated Tablet

III. Inlay tablets

A type of layered tablet in which instead the core tablet being completely surrounded by coating, top surface is completely exposed. While preparation, only the bottom of the die cavity is filled with coating material and core is placed upon it. When compression force is applied, some coating material is displaced to form the sides and compress the whole tablet. It has some advantages over compression coated tablets:

i) Less coating material is required.
ii) Core is visible so coreless tablets can be easily detected.
iii) Reduction in coating forms a thinner tablet and thus freedom from cappingof top coating.

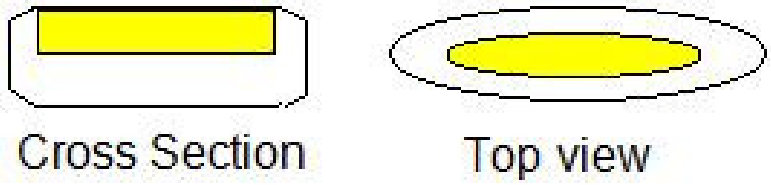


Figure No:4 Inlay Tablets

1.1.1.2 Standard compressed tablets

These are the standard uncoated tablets made by either direct compressionor wet granulation or dry granulation or double compaction.

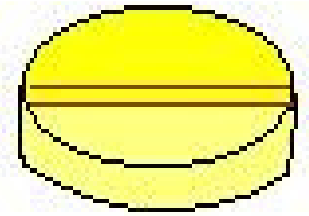


Figure No:5 Standard Compressed Tablet

They may be used for local action in gastro-intestinal tract or systemic action. When the tablet exert local action, they are formulated as more water insoluble by means of selecting slow dissolving excipients and thus provides local action for long time period. e.g., antacids and adsorbents. The drugs that produce systemic action have some aqueous solubility and designed to disintegrate and dissolve quickly so that the drug can be quickly absorbed and produce systemicaction. Generally, an API exhibits

bioavailability depending upon Biopharmaceutical Class, which is based on water solubility and gastro-intestinal membrane permeability criteria. But, it can be altered by appropriate selection of excipients and processing technology.

1.1.1.3 Modified Release tablets

The main aim behind formulation of this dosage form is to release the medicament Slowly for long time duration after administration of a single tablet.

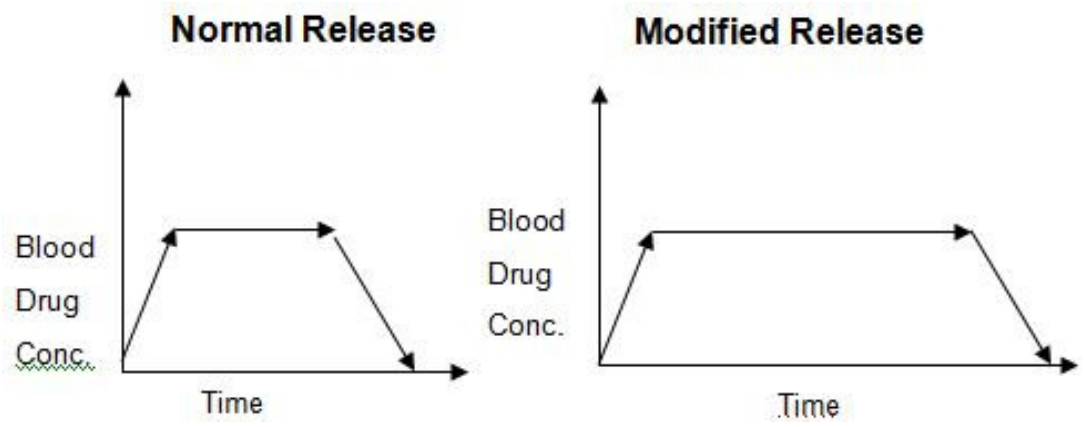


Figure No:6 Graphical Comparison of Blood Concentration Vs Time

A widespread use of this type of tablet is seen in present scenario, as well as many researchers have concentrated their attention in this direction. This is mainly because of improvement in patient's compliance as the dosage frequency is reduced, patient can take an undisturbed sleep at night, it's also beneficial for psychiatric patients who forget to take their tablets regularly and thedose related side effects and toxicities are reduced. Any adjuvant that can water uptake rate, swelling and gelling characteristics of Matrixing agents can alter the release rate of API e.g., electrolytes in HPMC matrix tablet. It's also possible to achieve pulsed drug release. Weakly basic drugs exhibit good solubility at low pH while less soluble at high pH conditions, which can result in incomplete drug release for sustained release formulations. The drug release can be modified by providing suitable micro environmental pH in the tablet e.g., acidic polymer, succinic acid, etc. Similarly, inclusion of alkaline polymers results in desirable drug release of acidic drugs. On the other hand, formulation of this type of dosage form presents challenge for the formulator increases the cost of manufacturing, chances of burst drug release and drop in drug release rate in terminal phase and thus incomplete release on API. In case of accidental poisoning, the doctor has to deal with special treatment problems. Due to large

size, patient may feel difficulties in swallowing as the matrixing agent to drug ratio is high. Classic approaches are usually based on adaptation of either film coated or multi particulate technologies or those involving slow release matrices. ***(Lachman L et. al)***

Coating technology

It combines semi permeable coatings and osmotic tablet cores to produce "zero order release" technology. Attention is also focused to trigger drug releaseat critical time point e.g., to achieve drug release 1-2 hours before the patient awakens. Alza's prolific research activities have yielded a technology called "Ringcap" which is based on a tablet, preferentially film coated, partially coated with a series of rings whose respective thickness provides the means of moderating the rate at which the drug is released from final dosage form.

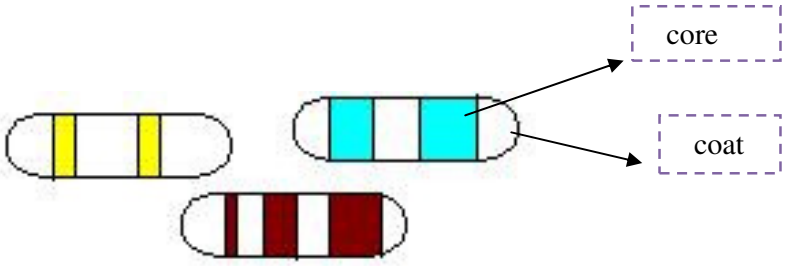


Figure No:7 Ringcap (Coated) Tablet

Matrix technology

Matrix products exhibit first order (or perhaps square-root-of-time)drug release characteristics. In order to achieve zero order release characteristics, it's necessary to employ specially designed materials or strategies that seekto manipulate tablet structure or geometry. Combination of conventional HPMC matrix technology with upper and lower layer. This helps to moderate drug release by increase in surface area with concomitant reduction in drug concentration within the device.

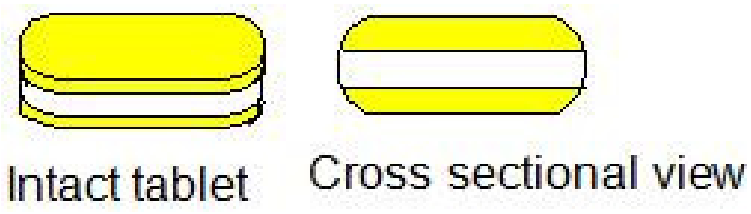


Figure No:8 Matrix Tablet

Releases of medicament can follow various mechanisms (2)

i) Diffusion is rate limiting

Diffusion is driving force where the movement of drug molecules occurs from high concentration in the tablet to lower concentration in gastro intestinal fluids. This movement depends on surface area exposed to gastric fluid, diffusion pathway, drug concentration gradient and diffusion coefficient of the system.

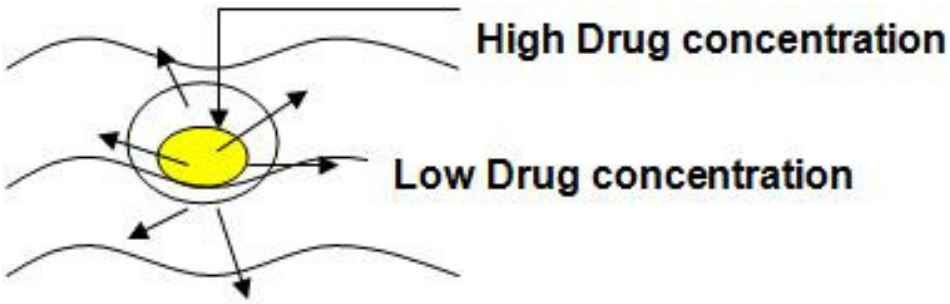


Figure No:9 Diffusion Release Pattern

In practice, we can follow either of the two methods,

1. The drug is formulated in an insoluble matrix; the gastric fluid penetrates the dosage form and dissolves the medicament and release the drug through diffusion.
2. The drug particles are coated with polymer of defined thickness so as the portion of drug slowly diffuse through the polymer to maintain constant drug level in blood.

ii) Dissolution is rate limiting

The drugs with poor water solubility (BCS class 2 and4) are inherently sustained release forms. While for water soluble drugs, it's possible to incorporate a water insoluble carrier to reduce dissolution of the drug particles are coated with this type of materials E.g. Polyethylene Glycol. One may skip the use of disintegrating agent to promote delayed release. ***(Lachman L et.al)***

iii) Osmotic pressure is rate limiting

Osmosis is a phenomenon in which the flow of liquid occurs from lower concentration to higher concentration through a semi permeable membrane which allows transfer of liquid only. The whole drug is coated with a semi permeable membrane with a hole on one end of tablet made by a laser beam. The gastric fluid penetrates through the

membrane, solubilizes the drug and increases the internal pressure which pumps the drug solution out of the aperture and releases the drug in gastric environment. The delivery rate is constant provided that the excess of drug present inside the tablet. But, it declines to zero once the concentration drops below saturation.

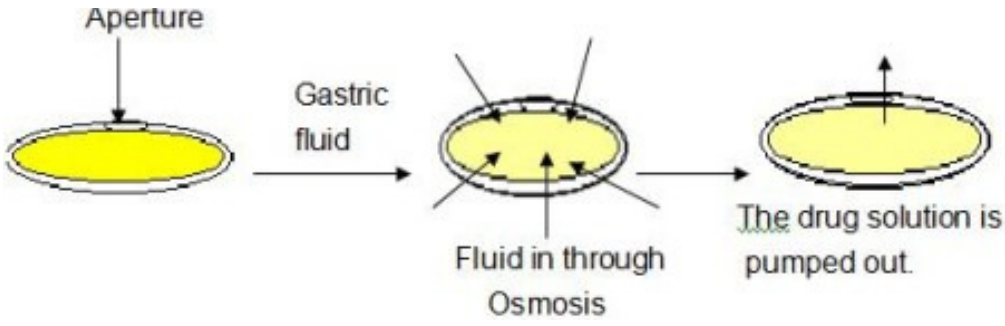


Figure No:10 Osmotic Release Pattern

iv) Release is controlled by ion exchange

Ion exchangers are water insoluble resinous materials containing salt forming anionic or cationic groups. While manufacturing, the drug solution is mixed with resin and dried to form beads which are tableted. The drug release depends upon high concentration of charged ions in gastrointestinal tract where, the drug molecules are exchanged and diffused out of the resin into the surrounding fluid. This mechanism relies upon the ionic environment of resin and not pH or enzyme on absorption site.(***Aulton M.)***

1.1.1.4 Delayed action tablets

Enteric coated tablet is such an example of delayed action tablet. This formulation is preferred when,

i) The API irritates gastric mucosa e.g., aspirin or strong electrolytes
ii) Drugs that produce nausea and vomiting.
iii) API is sensitive to low pH e.g., erythromycin
iv) When it's necessary to release the drug undiluted. e.g., intestinal antibacterial, antiseptic agents, intestinal vermifuge, etc.

The commonly used coating agents are: Cellulose acetate phthalate, Hydroxy methyl propyl phthalate, polyvinyl acetatephthalate, Eudragit®, etc. This dosage form is intended

to hydrateand begin to dissolve in duodenum (pH 4 to 6) or in small intestine where pH increases to 7 to 8. The presence of esterases or bile salts like surface active agents plays a role in drug release. ***(AultonM)***

1.1.1.5 Targeted tablets:

When we need to release the API at a specific site in the elementary tract, targeted drug delivery is a preferred option. Depending upon the composition and release mechanism of a tablet, the drug is delivered to a particular region. Under this category, we have two types of tablet

I. Gastro retentive Tablet

This type of dosage form is to be opted when API release is desired in stomach (Antacids, API used against *H.pylori* infection)or site of absorption is either stomach or upper part of small intestine.

Figure No:11 Floating Tablet

Retain the drug for longer time period in stomach,following approaches can be used:

i) Low density tablet (effervescent or non-effervescent)

ii) Tablets that can expand in gastric environment (swelling or by unfolding) and thus increasing the size so that itcannot cross the pyloric sphincter.

iii) Using muco-adhesive polymers that stick to mucosa of stomach and provide slow drug release.

Supine position is to be avoided and also high level of fluid is necessary or if the swelling formulation leaves stomach before it swells it's ineffective. Drugs like Diazepam, Levodopa, Benserazide, and Ciprofloxacin are successfully marketed in this formulation.

II. Colonic tablets

When the aim is to deliver the drug into colon without dilution in other regions of gastrointestinal tract or the drug has poor absorption in stomach or small intestine, colonic drug delivery is an answer of choice. The pH in this region varies from 6.4 - 7 and presence ofmicrobial flora plays as important role in drug release especially in this region. Various mechanisms are adopted for drug release in this area are coating with pH sensitive polymer e.g., Eudragit®S100, Eudragit® L100, biodegradable polymer like polymers which are sensitive to colonic bacteria,bioadhesive polymers which selectively sticks to colonic mucosa e.g.,polycarbophils or polyethans, redox sensitive polymers that respond to redoxpotential in colon which expresses the total metabolic and bacterial action.

1.1.1.6 Chewable tablets

The patients who have difficulty in swallowing tablets whole or for children who have not yet learnt to swallow a tablet chewable tablet serves as an attractive alternative. The added advantage ofthis medication is that it can be taken at any time or when water is not available. Mannitol is normally used as a base due to low hygroscopic and more importantly,it gives pleasant, cooling sensation. Antacid tablets are invariably prepared as chewable to obtain quick ingestion relief as well as the antacid dose is toolarge to swallow and the activity is related to particle size. Another exampleis multivitamin tablet which a patient can take as a daily dose. ***(Lachman L et.al)***

1.1.1.7 Dispersible tablet

These tablets disintegrate either rapidly in water,to form a stabilized suspension, or disperse instantaneously in the mouth to be swallowed without the aid of water. So, it's preferred for pediatric patientswho cannot swallow a solid dosage form and the API is unstable if formulated inliquid formulation. Also helpful for patients having prolonged illness who are prone to nauseatic sensations if they have to swallow a tablet. The added advantage of this formulation is faster onset of action as compared to standard compressed tablet. The properties of the water dispersible tablet, such as porosity,hardness, disintegration time have necessary to investigate during manufacturing which decides the product performance. The common examples of API formulated in this dosage form are analgesics e.g., aspirin, ibuprofen, etc.

1.1.2 Tablets used in the oral cavity

The tablets under this group are aimed release API inoral cavity or to provide local action in this region. The tablets under this category avoids first-pass metabolism, decomposition in gastric environment, nauseatic sensations and gives rapid onset of action. The tablets formulated for this region are designed to fit in proper region of oral cavity.

1.1.2.1 Lozenges and troches

The tablet is a flat faced at least about 18mm in diameter and meant to suck and dissolves in the mouth. The compressed tablet is called troches and the tablets produced by fusion or candy molding process are called lozenges. Flavours and sweeteners are added to make tablets palatable. The tablet generally contains sucrose or lactose and gelatin solution to impart smooth taste. Lozenges for local action in mouth/ throat are: antiseptics, antibiotics, demulcents, antitussive agents or astringents. To produce systemic action: multivitamin tablet. ***(AultonM)***

1.1.2.2 Sublingual tablets

They are to be placed under the tongue and produce immediate systemic effect by enabling the drug absorbed directly through mucosal lining of the mouth beneath the tongue.

Figure no:12Sublingual Tablets

The drug absorbed from stomach goes to mesenteric circulation which connects to stomach via portal vein. Thus, absorption through oral cavity avoids first-pass metabolism. The tablets are usually small and flat, compressed lightly to keep them soft. The tablet must dissolve quickly allowing the API to be absorbed quickly. It's designed to

dissolve in small quantity of saliva. After the tablet is placed in the mouth below the tongue, the patient should avoid eating, drinking, smoking and possibly talking in order to keep the tablet in place. Swallowing of saliva should also be avoided since the saliva may contain dissolved drug. Bland excipients are used to avoid salivary stimulation. Due to inconvenience in administration, this dosage form is prepared only for those API(s) for which the only satisfactory nonparenteral method is this route. For example, Glyceryltrinitrate (vasodilator) and Isoprinosinesulphate (bronchodilator). ***(AultonM)***

1.1.2.3 Buccal tablets

Completeness of drug absorption is desired but fast drug absorption is not intended. The tablets are designed not to disintegrate. They are flat elliptical or capsule shaped tablets as it can be easily held between gum and cheek. It's placed near the opening of parotid duct to provide the medium to dissolve the tablet.

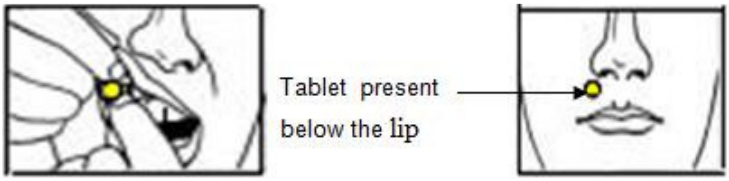


Figure no:13 Buccal Tablets

Since this tablet is to be kept for 30-60 minutes inoral cavity, care should be taken to see that all the ingredients are finely divided to avoid gritty or irritating sensation. This tablet is most often usedwhen replacement hormonal therapy is to be administered. Antifungal drugs are preferred to be administered by this route. e.g., Miconazole – under Clinical trial – still not available in market.

1.1.2.4 Dental cones

These tables are designed to be loosely packed in theempty socket remaining following a tooth extraction. Main purpose behind the use of this tablet is either to prevent multiplication of bacteria in the socket by employing a slow releasing antibacterial compound or to reduce bleeding by an astringent or coagulant containing tablet.

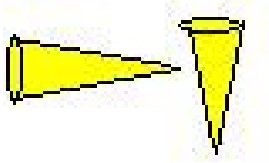


Figure no:14 Dental Cones

It's formulated to dissolve or erode slowly inpresence of a small volume of serum or fluid over 20-40 minutes period.

1.1.2.5 Mouth Dissolved tablets/ Rapidly Dissolving tablets

Known to the FDA as orally disintegrating tablets, they are also called mouth-dissolving, fast-dissolving, rapid-melt, porous, or dispersible, quick dissolving. These kinds of tablets are preferred when fast action or relief is desired. Most commonly used drugs under this formulation are the agents active against Migraine. The tablets are designed to disintegrate as well as dissolve within one minute or some within 10 seconds of oral administration in limited quantity of saliva. They liquefy on tongue and patient swallows the liquid, without the need of water. A number of techniques are used to prepare these tablets, including lyophilization, soft direct compression. Matrices having an API and high porosity are also being prepared using sublimation process. Urea, urethane, ammonium carbonate, ammoniumbicarbonate, hexamethylene, benzoic acid, naphthalene and camphor are commonly used for sublimation processing as they volatize rapidly. After removal by sublimation, these inert volatile substances leave the matrices with a high porosity. Disintegrants and sugar based excipients, such as sodium starchglycolate, cross carmellose sodium, mannitol, xylitol, dextrose, fructose, maltose and poly dextrose have been incorporated in almost all the orally disintegrating dosage forms (ODDFs). Loading of drug is made by preparing a blank and drug is post loaded. Generally the drug in solution is added after which the solvent evaporates. Taste masking poses numerous challenges since the drug product dissolves in mouth, any taste of drug must be covered, either by flavoring technique or by micro encapsulation or nano encapsulation. A major drawback of most of these systems is that the packaging system needs a higher degree of protection due to the lower hardness and more friability of the porous nature of tablets, except the DuraSolv technology of CIMA Labs, which are suitable for rigors of bulk bottle packaging. Keep the orally disintegrating tablet in the

blister pack inside the outer foil pouch until the patient is ready to take the medicine. Make sure that operator's hands are dry and peel opens the blister to remove the tablet. Place the tablet on tongue and let it dissolve. These dosage forms have become a delivery system of choice for most patients as they provide comfort for administration through out the day. Pharmaceutical companies, on the other hand, benefit from value addition in terms of product life-cycle management in today's market. ***(AultonM)***

1.1.3 Tablets administered by other routes

These tablets are administered by other route except for the oral cavity and so the drugs are avoided from passing through gastrointestinal tract. These tablets may be inserted into other body cavities ordirectly placed below the skin to be absorbed into systemic circulation from the site of application.

1.1.3.1 Vaginal tablets

This tablet undergoes slow dissolution and drug release in vaginal cavity of women. The shape is kept ovoid or pear shaped to facilitate retention in vagina. The tablet should be made compatible with plastic tube inserters who are designed to place the tablet in the upper region of vaginal tract. These tablets generally release antibacterial, antiseptics or astringents to treat vaginal infections or release steroids for systemic absorption.

1.1.3.2 Implants

These tablets are inserted into subcutaneous tissue by surgical procedures where they are very slowly absorbed over a period of a month or a year. A special injector with a hollow needle and plunger is used to administer the rod shaped tablet for other shapes, surgery is required. The tablets may be pellet, cylindrical or rosette shaped with diameter not more than 8mm. They are sterile formulation without excipients and made hard with large particle size to achieve gradual drug release. The tablets are produced by a sterile single punch hand operated machine in which the die cavity is filled with hand since the material does not normally flow well. Mainly, these tablets are prepared to deliver growth hormones to food producing animals and ear is the preferred site for administration of the drug.

1.1.4 Tablets used to prepare solution

The tablets under this category are required to be dissolved first in water or other solvents before administration or application. This solution may be for ingestion or parenteral application or for topical use depending upon type of medicament used.

1.1.4.1 Effervescent tablets

The oral dosage forms are the most popular way of taking medication despite having some disadvantages like slow absorption and thus onset of action is prolong. This can be overcome by administrating the drug in liquid from but, many APIs have limited level of stability in liquid form. So, effervescent tablets acts as an alternative dosage form. The tablet

is added into a glass of water just before administration and the drug solution or dispersion is to be drunk immediately. The tablet is quickly broken apart by internal liberation of CO2 in water due to interaction between tartaric acid and citric acid with alkali metal carbonates or bicarbonates in presence of water. (***Rawlins EA editor, 1995).***

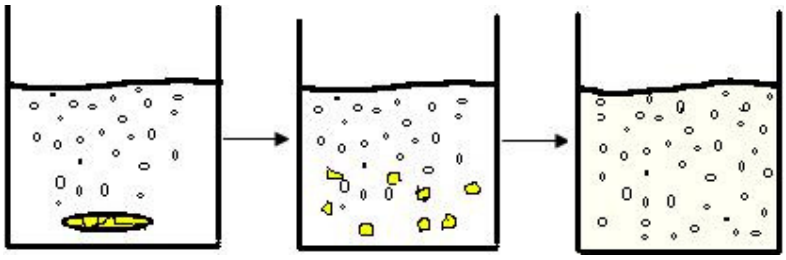


Figure no:15 Effervescent Tablets

Due to liberation in CO2 gas, the dissolution of API in water as well as taste masking effect is enhanced. The advantages of effervescent tablets compared with other oral dosage forms includes an opportunity for formulator to improve taste, a more gentle action on patient's stomach and marketing aspects. To manufacture these tablets, either wet fusion or heat fusion is adopted. The tablets are compressed soft enough to produce an effervescent reaction that is adequately rapid. Water soluble lubricants are used to prevent an insoluble scum formation on water surface. To add sweetness to the formulation, saccharin is added since sucrose

is hygroscopic and add too much of bulk to the tablet. The manufacturing shall be done under controlled climatic condition to avoid effervescent reaction. The packaging is done

under 25% RH at 25ºC. Hands of the consumers and atmospheric moisture after opening the container can also result in loss of product quality. The most commonly used effervescent tablet today is aspirin tablet. ***(Lachman L., Liberman L)***

1.1.4.2 Hypodermic tablets

These tablets contain one or more readily water soluble ingredients and are intended to be added in water for injection of sterile water to form a clear solution which is to be injected parentally. They were widely used by rural physician due to its portability. One bottle of sterile water was carried by the doctor to prepare many types of injectables. It can be used for medicaments whose stability in water is very poor.

1.1.4.3 Soluble tablets

Tablets are pre-formed solids of uniform shape and dimensions, usually circular, with either flat or convex faces, the distance between faces being less than the diameter. Water soluble tablets are intended for application after dissolution in water and contain an active ingredient should be totally soluble in water at used concentrations. All the excipients used to formulate these tablets are required to be completely soluble in water including the glidants, binders, etc. So, manufacturing of this kind of tablets are challenge for the formulator.

Companies manufacturing these tablets have patented them.

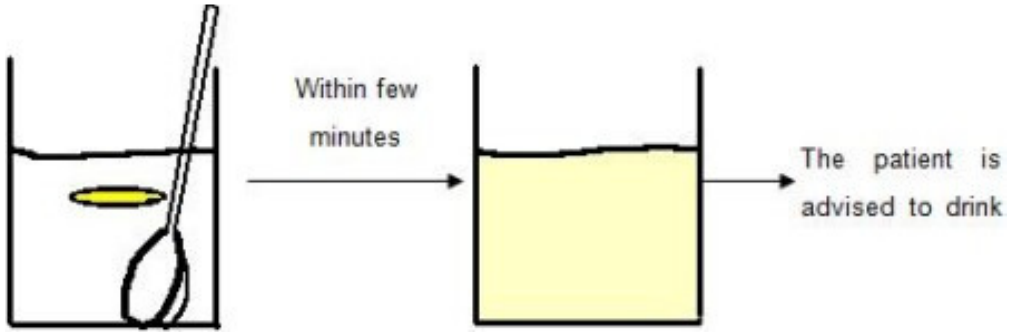


Figure no:16 Soluble Tablets

1.2 Manufacturing Methods

There are three general methods of tablet preparation.

- Direct compression method
- Dry granulation method
- Wet granulation method

1.2.1 Direct compression

Direct compression is the process by which tablets are compressed directly from powder mixture of API and suitable excipients. This method of tablet making is of special interest for small group of crystalline chemicals having the entire physical characteristic necessary for the formulation of a good tablet. ***(Martinello T,2006)***

1.2.2 Dry granulation method

This process of granulation is also known as Slugging, double compression or recompression method. This process of tablet preparation is commonly used when the tablet ingredients are sensitive to moisture or are unable to withstand elevated temperature during drying. Under such conditions dry granulation is the method of choice provided the tablet ingredients have sufficient inherent binding or cohesive properties.

1.2.3 Wet granulation method

Wet granulation process simply involves wet massing of the powder blend with a granulating liquid, wet sizing and drying. (***Rawlins EA editor, 1995).***

1.3 Acceptance Criteria for Tablets/Granules

Bulk density values having less than 1.2 g/cm^3 indicates good packing and values greater than 1.5 g/cm^3 indicates poor packing of tablets. Tablets having values of more than 5kg/cm^2 indicate good hardness property and the friability limit should be below 1%.

Acceptance criteria for flow properties of granules like Angle of repose, Compressibility index, Hausners ratio is given in the Table 2 and weight variation of tablets is given in the Table 3.

TABLE :2 ACCEPTANCE CRITERIA OF FLOW PROPERTIES

Compressibility Index	Angle of Repose Range (^{0})	Hausner Ratio	Flow Character
1 – 10	25 – 30	1.00 – 1.11	Excellent
11 – 15	31 – 35	1.12 – 1.18	Good
16 – 20	36 – 40	1.19 – 1.25	Fair
21 – 25	41 - 45	1.26 – 1.34	Passable
26 – 31	46 – 55	1.35 – 1.45	Poor
32 – 37	56 – 65	1.46 – 1.59	Very Poor
> 38	> 66	> 1.60	Very Very Poor

TABLE: 3 ACCEPTANCE CRITERIA FOR WEIGHT VARIATION

Average weight of tablet (mg)	Percentage difference allowed
≤130	10
130-324	7.5
>324	5

1.4 Hypertension Epidemiology

Cardiovascular diseases such as coronary heart disease and stroke are the largest causes of death in developing countries and are one of the main contributors to disease burden. Between years 1990 and 2020 these diseases are anticipated to increase by 120% for women and 137% for men in developing countries. In India about 70% of coronary heart disease-related deaths occur in people younger than 70 years compared with 22% in the west and 94% stroke deaths occurs in people less than 70 years in contrast to 6% in developed countries. Blood pressure (BP) is directly associated with risks of several types of cardiovascular diseases and the associations of BP with disease risk are continuous with large proportions of most populations having non-optimal blood pressure values. In India cardiovascular diseases cause 5 million deaths annually. Hypertension is directly responsible for 57% of all stroke deaths and 24% of all coronary heart disease deaths. This fact is important because hypertension is a controllable disease and a 2 mm Hg population wide decrease in BP can prevent 151,000 stroke and 153,000 coronary heart disease deaths. Better control can lead to prevention of 300,000 of the 1.5 million annual deaths from cardiovascular diseases in India. ***(Rajeev.G,et al,2009).***

1.5 Etiology of Hypertension

Blood pressure is the force with which blood pushes against the artery walls as it travels through the body. Blood pressure is measured by two numbers systolic pressure and diastolic pressure. Systolic pressure measures cardiac output and refers to the pressure in the arterial system at its highest. Diastolic pressure measures peripheral resistance and refers to arterial pressure at its lowest. Blood pressure is normally measured at the brachial artery with a sphygmomanometer (pressure cuff) in millimeters of mercury (mm Hg) and given as systolic over diastolic pressure. The upper number is the systolic pressure, which is the peak force of blood as the heart pumps it. The lower number is the diastolic pressure, which is the pressure when the heart is filling or relaxing before the next beat. Normal blood pressure for an adult is 120/70 (on average) Hypertension, or high blood pressure, is defined as a reading of 140/90 on three consecutive measurements at least six hours apart. Hypertension is a major cause of stroke. ***(eHow,2011)***

1.6 Types of Hypertension

There are two major types of hypertension and four less frequently found types. The two major types are:

1. Primary or essential hypertension
2. Secondary hypertension

The other types include:

- Malignant Hypertension.
- Isolated Systolic Hypertension
- White Coat Hypertension
- Resistant Hypertension

1.6.1 Primary or essential hypertension

Primary hypertension has no specific origin but is strongly associated with lifestyle. It is responsible for 90 to 95 percent of diagnosed hypertension and is treated with stress management, changes in diet, increased physical activity and medication.

1.6.2 Secondary hypertension

Secondary hypertension is responsible for 5 to 10 percent of diagnosed hypertension. It is caused by a preexisting medical condition such as congestive heart failure, kidney failure, liver failure, or damage to the endocrine (hormone) system.***(Ehow,2011)***

1.7 Stages of Hypertension

The concept of "stage of hypertension" was determined in the U.S. by the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure .

There are three stages of hypertension:

1. Prehypertension
2. Stage 1 Hypertension
3. Stage 2 Hypertension

Table:1 Categories For Blood Pressure Levels In Adults

	Blood Pressure Level (mmHg)		
Category	**Systolic**		**Diastolic**
Normal	< 120		< 80
Prehypertension	120-139		80-89
High Blood Pressure			
Stage 1 Hypertension	140–159		90–99
Stage 2 Hypertension	≥160		≥100

1.8 Treatment of hypertension

Medications that lower blood pressure are often referred to as antihypertensive drugs. Generally these drugs are classified

- Diuretics
- Beta-adrenergic blocking agents
- Calcium channel blockers
- Angiotensin converting enzyme (ACE) inhibitors
- Angiotensin II Receptor Blockers (ARBs)
- Vasodilators

Angiotensin II Receptor Blockers (ARBs)

The renin-angiotensin system, specifically angiotensinII, is implicated in the pathogenesis of essential hypertension, renovascular hypertension, congestive heart failure, and renal diseases associated with albuminuria. Blockade of the rennin-angiotensin system with ACE inhibitors has provided effective treatment of these conditions; however, some of the adverse effects of ACE inhibitors appear to be unrelated to angiotensin II blockade. For example, cough and angioedema are due to other effects of ACE inhibition, such as degradation of bradykinins and prostaglandins.

ARBs are used for controlling high blood pressure, treating heart failure and preventing kidney failure in people with diabetes or high blood pressure. They may also

prevent diabetes and reduce the risk of stroke in patients with high blood pressure and an enlarged heart. ARBs may also prevent the recurrence of atrial fibrillation. ***(Rajeev.G,et al,2009).***

ARBs have the following actions

- Dilate arteries and veins and thereby reduce arterial pressure and preload and afterload on the heart.
- Down regulate sympathetic adrenergic activity by blocking the effects of angiotensin II on sympathetic nerve release and reuptake of norepinephrine.
- Promote renal excretion of sodium and water (diuretic effects) by blocking the effects of angiotensin II in the kidney and by blocking angiotensin II stimulation of aldosterone secretion.
- Inhibit cardiac and vascular remodeling associated with chronic hypertension, heart failure, and myocardial infarction.

2. LITERATURE REVIEW

McClellan.K *et.al.,*(1998) revealed that candesartan cilexetil is effective and well tolerated when used once daily (as monotherapy or in combination with other antihypertensive agents) in patients with mild, moderate or severe hypertension. once daily, oral candesartan cilexetil 8 to 32mg dose-dependently and effectively reduces blood pressure in patients with mild to moderate essential hypertension. One study showed candesartan cilexetil 16 mg/day to be more effective than losartan potassium 50 mg/day. Furthermore, the combination of candesartan cilexetil with either hydrochlorothiazide or amlodipine resulted in additive antihypertensive effects. Pooled data indicate that the tolerability profile of the drug is not significantly different from that of placebo, with headache being the most commonly reported event. Adverse events are not dose related and are mostly mild to moderate in severity. Candesartan cilexetil is better tolerated than enalapril, primarily because of a reduced incidence of cough, and was not associated with the hypokalaemia or hyperuricaemia seen with hydrochlorothiazide in a study in patients aged ≥75 years.

Stoukides.C *et.al.,*(1999) reported that candesartan cilexetil provides an alternative antihypertensive therapy that is well tolerated and effective in reducing blood pressure in a wide range of patients. Due to its greater binding affinity to the angiotensin II receptor, candesartan cilexetil appears to have a longer antihypertensive effect than losartan.The study showed that Candesartan cilexetil has demonstrated reductions in blood pressure comparable to those of enalapril, with the rate of adverse events greater in the enalapril group.

Erdmann *et.al.,*(2000) revealed that candesartan cilexetil is safe when compared with placebo in the treatment of patients with CHF. This study involved a blinded, independent review of all adverse event data and was performed to assess all-cause mortality and unexpected deaths, and hospitalizations for acute deterioration of CHF, chronic progression of CHF, other intercurrent events, or accidental injury/attempted suicide. The descriptive analysis included crude and cumulative incidence rates for mortality and cardiac and non-cardiac morbidity using the Kaplan-Meier method and the log-rank test. The results demonstrated a clinically non-significant trend for all relevant events.

Homma.K ***et.al.,*****(2004)** revealed that combination therapy with ARB plus ACEI/amlodipine proves beneficial than the ARB monotherapy in nondiabetic renal disease. Present study compared the effect of the combination therapy with ARB plus calcium antagonists/ACEI on proteinuria with that of the ARB monotherapy in chronic nondiabetic renal disease. At 1 month of the drug treatment, the candesartan monotherapy (n=19) reduced BP from 154±3/93±2 to 146±3/88±2 mmHg ($P<0.05$), and a similar magnitude of BP reductions was observed with the combination therapy with candesartan plus ACEI/amlodipine (from 153±2/95±2 to 144±2/88±2 mmHg, $P<0.05$, n=39). In contrast, the reduction in proteinuria was greater with the combination therapy (-52±3% at 12 months, n=39) than with the candesartan monotherapy (-25±3%, n=19) Since the reduction in BP was achieved to the same level, the distinct proteinuria-sparing action of these therapies is attributed to BP-independent mechanisms, which should vary depending on the agents used.

Pfister ***et.al.,*****(2004)** reported that HD does not influence the elimination kinetics of candesartan. The observed inter- and intra individual variability of oral clearance and the pronounced influence of HD-induced volume contraction on the haemodynamic effects of candesartan makes it mandatory to carefully monitor HD patients treated with candesartan cilexetil. It was a repeated dose study (8 mg candesartan cilexetil once daily) in eight male HD patients over a treatment period of 5 days with an additional observation period of 3 days. Pharmacokinetic analysis with nonlinear mixed effects modeling (NONMEM) over the whole treatment period revealed a dependency of the volume of distribution on body weight and of the metabolic clearance on age and body weight in the studied population. No significant drug elimination by HD was observed.

Graham.A ***et.a.l,*****(2004)** revealed that candesartan cilexetil is an effective BP-lowering drug when used alone or in combination with amlodipine or amlodipine plus hydrochlorothiazide in the treatment of moderate-to-severe essential hypertension. This study evaluated the efficacy of candesartan cilexetil, an angiotensin II type 1 receptor antagonist, used alone or in combination with amlodipine or in combination with amlodipine and hydrochlorothiazide in the treatment of patients with moderate-to-severe essential hypertension. The result of the study demonstrated that candesartan is an effective BP-lowering drug when used alone or in combination with amlodipine or amlodipine plus hydrochlorothiazide and was well tolerated throughout the investigation.

Toblli.J *et.al.,*(2004) reported that candesartan cilexetil provides a significant protective role against morphologic changes in vessels as well as in cavernous spaces of the erectile tissue, caused by high blood pressure, in SHR. This present study was performed to determine whether an angiotensin II receptor blocker could protect cavernous tissue (CT) from these structural alterations in SHR.Male SHR and Wistar-Kyoto (WKY) rats were studied during 4 months. Rats were divided into three groups: SHR (*n*=10), SHR with candesartan cilexetil (*n*=10) and WKY rats (*n*=10). Candesartan cilexetil 7.5 mg/kg/day was administered orally throughout the study. CT was processed for pathology studies. The amount of (1) cavernous smooth muscle (CSM), (2) vascular smooth muscle (VSM), (3) collagen type III, and the rat endothelial cell antibody (RECA-1)/tunica media ratio in cavernous arteries were evaluated.

See.S *et.al.,*(2008) reported that candesartan cilexetil is an effective antihypertensive agent that can be used alone or in combination with other antihypertensive drugs. It is generally well tolerated and may be an option for patients who cannot tolerate angiotensin-converting-enzyme inhibitors because of cough. In clinical trials, candesartan cilexetil has produced a dose-dependent effect when given in dosages of 2-32 mg/day. Observed trough-to-peak blood pressure ratios support a once-daily dosage regimen. The antihypertensive effect of candesartan cilexetil 4-16 mg/day was as great as that of enalapril 10-20 mg/day and amlodipine 5 mg/day and larger than that of losartan potassium 50 mg/day. Adding candesartan cilexetil to hydrochlorothiazide 12.5-25 mg/day and amlodipine 5 mg/day led to enhanced blood-pressure reductions and was well tolerated.

Vijay.N *et.al.,*(2008) revealed that the wet bead milling process coupled with spray granulation is a viable approach for developing nanoparticle formulations of biopharmaceutics classification system (BCS) class II compounds with enhanced solubility and faster dissolution. In this study the granules containing drug nanoparticles of KC, FF and CC were blended with extra-granular excipients using a double cone blender. The blend was subsequently compressed into tablets at the desired strength, and the physical properties of tablets — hardness, friability and disintegration time — were measured. Enhancing solubility and dissolution velocity of sparingly soluble compounds correlates with an improved pharmacokinetics profile and a concomitantly improved therapeutic outcome.

Franks *et.al.,*(2008) reported that candesartan cilexetil effectively reduced BP as demonstrated by CBPM and ABPM measurements and was well tolerated in this group of hypertensive children. In this study, eleven patients (mean age 14.2 y) received a final candesartan cilexetil median daily dose of 8 mg (0.13 mg/kg, range 2–16 mg). Study treatment resulted in significant reductions in systolic and diastolic BP as measured by CBPM (–7.4%, p = 0.03 and –5.9%, p = 0.01, respectively) and by ABPM (–6.0%, p = 0.03 and –10.8%, p = 0.006, respectively), but no significant reductions as measured by HBPM. No clinically significant changes in laboratory measures were observed and patients reported nonspecific mild adverse effects.

See.S *et.al.,*(2008) reported that candesartan cilexetil is an effective antihypertensive agent that can be used alone or in combination with other antihypertensive drugs. It is generally well tolerated and may be an option for patients who cannot tolerate angiotensin-converting-enzyme inhibitors because of cough. In clinical trials, candesartan cilexetil has produced a dose-dependent effect when given in dosages of 2-32 mg/day. Observed trough-to-peak blood pressure ratios support a once-daily dosage regimen. The antihypertensive effect of candesartan cilexetil 4-16 mg/day was as great as that of enalapril 10-20 mg/day and amlodipine 5 mg/day and larger than that of losartan potassium 50 mg/day. Adding candesartan cilexetil to hydrochlorothiazide 12.5-25 mg/day and amlodipine 5 mg/day led to enhanced blood-pressure reductions and was well tolerated.

Jean.B *et.al.,*(2009) revealed that candesartan significantly reduces the incidence of cardiovascular death, hospital admissions for decompensated heart failure, and all-cause mortality in chronic heart failure patients with altered left ventricular systolic function, when added to standard therapies or as an alternative to ACE inhibitors when these are poorly tolerated.Furthermore, the study showed that candesartan can protect against myocardial infarction, atrial fibrillation and diabetes. Tolerance to candesartan is good, but blood pressure and serum potassium and creatinine levels must be monitored.

Baguet.J *et.al.,*(2009) reported that candesartan and amlodipine besylate treatments may alter identically the natural progression of carotid IMT in hypertensive type 2 diabetic patients. This study consists of 36 months and investigated the effect of candesartan cilexetil(CC) on the common carotid intima-media thickness (IMT) vs amlodipine besylate (AML) in patients with type 2 diabetes and mild to moderate essential

hypertension.No significant differences were observed between the two groups for change in IMT at M12 (−0.001 vs −0.027 mm/year for CC and AML respectively, p = 0.425), at M24 (−0.033 vs −0.019 mm per year respectively, p = 0.442). The augmentation in carotid lumen diameter from baseline was statistically greater in the AML group at the last visit (p = 0.034). BP variations during the study were similar in the two groups.

Fang .G *et.al.,*(2010) reported that the nanoemulsion was very effective for enhancing the oral absorption of insoluble candesartan cilexetil, candesartan cilexetil loaded nanoemulsionshowed the great potential for clinical application. In this work, a novel candesartan cilexetil loaded nanoemulsion (CCN) was designed to improve the intestinal absorption. candesartancilexetil loaded nanoemulsion was prepared by a modified emulsification-solvent evaporation technique. The physicochemical characteristics of candesartan cilexetil loaded nanoemulsion were characterized, and the intestinal absorption was investigated as well. The experimental results indicated that candesartan cilexetil loaded nanoemulsion was nanometer-sized droplets (35.5 ± 5.9 nm) with negative potential (− 6.45 ± 0.36 mV), and the absorption of candesartan cilexetil loaded nanoemulsion was significantly improved in total intestinal tract compared with free candesartan cilexetil solution. The experimental results showed that the area under the concentration–time curve (AUC0–t) of candesartan was improved over 10-fold after candesartan cilexetil was incorporated into candesartan cilexetil loaded nanoemulsion..

Omari *et.al.,*(2010) revealed that complex formation of candesartan with β-cyclodextrins prepared by freeze drying method is chemically not stable due to the formation of amorphous candesartan and compression enhances the instability of candesartan. In this study the DSC thermograms for CAND/β-CyD complexes proved the formation of inclusion complexes with new solid phase. MM studies indicate the partial penetration of candesartan into the β-CyD cavity.

Akira.M,(2010) reported that candesartan cilexetil, 8 mg/day, significantly reduced the progression of CHF when compared with placebo. This 6-month study examined the safety and efficacy of candesartan cilexetil, 8 mg once daily, to prevent the progression of congestive heart failure (CHF).

3.AIM & OBJECTIVES

Aim:

The aim of the present study is to develop and evaluate candesartan cilexetil tablets with respect to reference sample. The formulation of tablets were done match the in-vitro drug release with respect to the reference drug and carry out stability studies .

Objective:

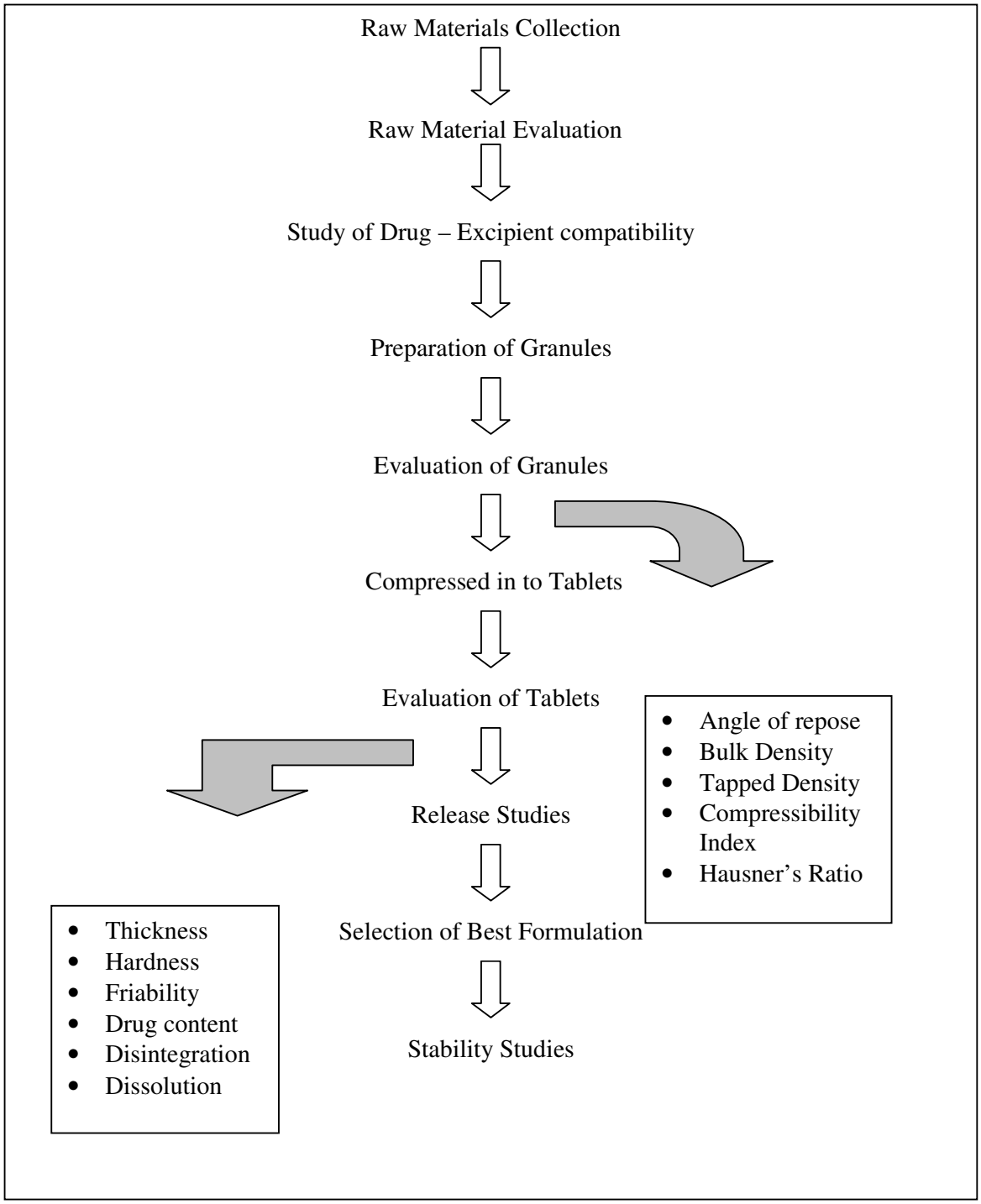
1. To formulate and evaluate immediate release candesartan cilexetil tablets (32mg).

Specific Objectives:

1. To perform preformulation studies including drug – excipient compatibility study.
2. To develop various formulations with different excipients.
3. To establish the invitro release compliance with the established criteria.
4. To establish the stabilityof the formulation.

4.PLAN OF WORK

Figure No:17 Plan of Work



5.EXPERIMENTAL INVESTIGATION

5.1 DRUG PROFILE

Physiochemical, Pharmacological and Pharmacokinetic nature of the candesartan cilexetilis given in Tables 4 - 6.***(Merk Manuals,2009).***The reference product specifications are given in Table 7.

TABLE: 4 PHYSIOCHEMICAL NATURE OF CANDESARTAN

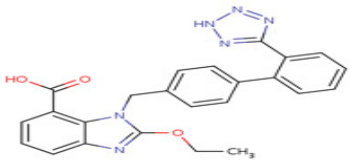
S.No	Physiochemical Nature	Description
1	Common Name	Candesartan cilexetil
2	Nature	Prodrug
3	State	Solid
4	Colour	White to off white
5	Taste	Sour to bitter
6	IUPAC Name	2-ethoxy-3-[[4-[2-(2H-tetrazol-5 yl)phenyl]phenyl]methyl]benzimidazole-4-carboxylic acid
7	Molecular Formula	$C_{24}H_{20}N_6O_3$
8	Chemical Structure	
9	Molecular Weight	610.659660 [g/mol]
10	Melting Point	163^0C
11	Solubility	Sparingly soluble in methanol, insoluble in water
12	Predicted Water Solubility	7.71 mg/mL

TABLE: 5 PHARMACOLOGICAL NATURE OF CANDESARTAN

S.No	Pharmacological Nature	Description
1	Indication	For the treatment of hypertension and Heart Failure.
2	Mechanism of Action	Candesartan competes with angiotensin II for binding at the AT1 receptor subtype. As angiotensin II is a vasoconstrictor which also stimulates the synthesis and release of aldosterone, blockage of its effects results in a decrease in systemic vascular resistance.
3	Drug Interactions	Amiloride — Increased risk of hyperkaliemia Drospirenone — Increased risk of hyperkaliemia Lithium — The ARB increases serum levels of lithium Potassium — Increased risk of hyperkaliemia Spironolactone — Increased risk of hyperkaliemia Triamterene — Increased risk of hyperkaliemia
4	Phase 1 Metabolizing Enzymes	Cytochrome P450 11B2 (CYP11B2)
5	Targets	Type-1 angiotensin II receptor
6	BCS	Class II - Low Solubility and High Permeability

(Ogihara T, 1994)

TABLE:6 PHARMACOKINETIC NATURE OF CANDESARTAN

S.No	Pharmacokinetic Nature	Description
1	Absorption	Bioavailability is about 15%
2	Distribution	Vd is 0.13 L/kg
3	Metabolism	Candesartan cilexetil is bioactivated by ester hydrolysis during absorption from the GI tract to candesartan. Candesartan undergoes minor hepatic metabolism by O-deethylation to an inactive metabolite
4	Elimination	Primarily as unchanged drug in the urine and by the biliary route, in the feces. Plasma Cl is 0.37 mL/min/kg. Renal Cl is 0.19 mL/min/kg. About 26% is excreted unchanged in urine.
5	T_{max}	3 to 4 hrs
6	Half Life ($t_{½}$)	9 hrs
7	Protein binding	More than 99%
8	Toxicity	No lethality was observed in acute toxicity studies in mice, rats and dogs given single oral doses of up to 2000 mg/kg of candesartan cilexetil

(Van Lier Jet.al,1997)

TABLE:7 REFERENCE PRODUCT SPECIFICATIONS OF CANDESARTAN

S.No	Product Specifications	Description
1	Drug Type	Approved
2	Dosage Form	Tablet
3	Route of Administration	Oral
4	Strength	4mg, 8mg, 16mg and 32mg
5	Non active Ingredients	Calcium CMC, maize starch, HPC, iron oxide lactose, magnesium stearate, PEG, Avicel.
6	Package	Blister Pack
7	Storage Conditions	Controlled room temperature
8	Available Brands	Amias, Atacand, Blopress, Ratacand

5.2 EXCIPIENT PROFILE

A. MICROCRYSTALLIN CELLULOSE:

Synonyms: Avicel PH, Celex, Cellulose gel, Celphere, Ceolus KG, crystalline cellulose.

Functional Category: Adsorbent, suspending agent, tablet and capsule diluent, tablet disintegrant.

Applications: Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting.

Description: Microcrystalline cellulose is purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Stability and Storage Conditions: Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

Solubility: Slightly soluble in 5% w/v NAOH solution, practically insoluble in water, diluent acids and most organic solvents.

Stability: It is stable though Hygroscopic material.

Incompatibilities: Microcrystalline cellulose is incompatible with strong oxidizing agents***(Raymond.C et al,2009)***

B. STARCH PREGELATINIZED

Synonyms: Compressible starch, Instastarch

Description: Pregelatinized starch occurs as a moderately coarse to fine, white to off-white colored powder. It is odorless and has a slight characteristic taste.

Functional Category: Tablet and capsule diluent, tablet and capsule disintegrant; tablet binder.

Applications: Pregelatinized starch is a modified starch used in oral capsule and tablet formulations as a binder, diluent, and disintegrant.

Stability and Storage Conditions: Dry, unheated starch is stable if protected from high humidity. When used as a diluent or disintegrant in solid-dosage forms, starch is considered to be inert under normal storage conditions. However, heated starch solutions or pastes are physically unstable and are readily attacked by microorganisms to form a wide variety of starch derivatives and modified starches that have unique physical properties. Starch should be stored in an airtight container in a cool, dry place***.(Raymond.C et al,2009)***

C. HYDROXYPROPYL CELLULOSE

Synonyms: Cellulose, hydroxypropyl ether; hydroxypropylcellulosum; hyprolose; klucel

Functional Category: Coating agent; emulsifying agent; stabilizing agent; suspending agent; tablet binder; thickening agent; viscosity-increasing agent.

Description: Hydroxypropyl cellulose is a white to slightly yellow-colored, odorless and tasteless powder

Applications: In oral products, hydroxypropyl cellulose is primarily used in tableting as a binder, film-coating and extended-release-matrix former. Concentrations of hydroxypropyl cellulose of 2–6% w/w may be used as a binder in either wet-granulation or dry, direct compression tableting processes.

Stability: Hydroxypropyl cellulose powder is a stable material, although it is hygroscopic after drying.

Incompatibilities: Hydroxypropyl cellulose in solution demonstrates some incompatibility with substituted phenol derivatives, such as methyl paraben and propyl paraben. ***(Raymond.C et al,2009)***

D. LACTOSE MONOHYDRATE

Synonyms: CapsuLac; GranuLac; Lactochem; lactosummonohydricum; Monohydrate; Pharmatose; PrismaLac; SacheLac

Functional Category: Dry powder inhaler carrier; lyophilization aid; tablet binder; tablet and capsule diluent; tablet and capsule filler.

Applications: Lactose is widely used as a filler and diluent in tablets and capsules, and to a more limited extent in lyophilized products and infant formulas.

Description: Lactose occurs as white to off-white crystalline particles or powder. Lactose is odorless and slightly sweet-tasting.

Storage: Mold growth may occur under humid conditions (80% relative humidity and above). Lactose may develop a brown coloration on storage.

Incompatibilities: A Maillard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown or yellow-brown-colored products.. ***(Raymond.C et al,2009)***

E. CALCIUM CARBOXYMETHYLCELLULOSE

Synonyms: Calcium carboxymethylcellulose; calcium cellulose glycolate; carmellosum calcium; CMC calcium

Functional Category: Emulsifying agent; coating agent; stabilizing agent; suspending agent; tablet and capsule disintegrant; viscosity-increasing agent; water-absorbing agent.

Applications: The main use of carboxymethylcellulose calcium is in tablet formulations as a binder, diluent, and disintegrant.

Description: Carboxymethylcellulose calcium occurs as a white to yellowish white, hygroscopic, odorless powder.

Stability and Storage Conditions: Carboxymethylcellulose calcium is a stable, though hygroscopic material. It should be stored in a well-closed container in a cool, dry place.

F. MAGNESIUM STEARATE

Synonyms: Dibasic magnesium stearate; magnesium distearate; magnesiistearas; magnesium octadecanoate; octadecanoic acid

Functional Category: Tablet and capsule lubricant.

Description: Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste.

Applications: It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w.(***Raymond.C et al,2009)***

5.3 MATERIALS AND METHODS

TABLE: 8 MATERIALS USED IN THE FORMULATION

S.No	Ingredients	Rationale	Source
1.	Candesartan Cilexetil	API	Aurabindo Pharmaceutical co.ltd Hyderabad
2.	Lactose Monohydrate	Diluent	Avon organics Ltd Mumbai
3.	Pre GelatinizedStarch	Filler/Binder	Aurabindo Pharmaceutical Ltd Hyderabad
4.	Microcrystalline cellose (Avicel PH 101)	Disintegrant	SD Fine Chemicals ltd Mumbai
5.	Klucel– LF	Binder	SD Fine Chemicals ltd Mumbai
6	Calcium. CarboxyMethyl Cellulose	Superdisintegrants	SD Fine Chemicals ltd Mumbai
7	Mg. Stearate	Glident	SD Fine Chemicals ltd Mumbai
8	Purified water	Solvent	NATCO Pharma Ltd Hyderabad
9	PEG 6000	Suspending agent	SD Fine Chemicals ltd Mumbai
10	Ferric oxide	Coloring agent	SD Fine Chemicals ltd Mumbai
11	Pvp-k30	Binder	SD Fine Chemicals ltd Mumbai

The list of equipments used for the formulation of candesartan immediate release tablets are given in Table.

TABLE:9 EQUIPMENTS USED FOR THE FORMULATION

Name of instrument	Model no.	Make
Electronic Weighing Balance	PR 203	Mettler Toledo Mumbai
Tap Density Tester USP	ETD-1020	Electrolab Mumbai
Electromagnetic Sieve Shaker	EMS-8	Electrolab Mumbai
Electronic Moisture Analyzer	HG 63	Mettler Toledo Mumbai
Tablet Compression Machine-8 station	MINI Press - II MT	Rimek Gujarat
Digital Hardness Tester	TH 10503	Labindia Bangalore
Disintegration Test Apparatus USP	ED-2AL	Electrolab Mumbai
Friabilator USP	EF-2	Electrolab Mumbai
Mechanical Stirrer	RQT-124D	Remi Motors Mumbai
Pharma R&D Coater	Deluxe	Ideal Cures Mumbai
Fluid Bed Drier	UT-150	UmangPharmatech Mumbai
Rapid mixture granulator	RMG 25	Anchormark Mumbai
Multi Mill	MM 15	Anchormark Mumbai
Weighing balance	T-26I	Scaletec Instruments (Citizen) Mumbai
Tray Drier	PPT TD6	Platinum Pharmatech Mumbai
Dissolution Test Apparatus Type II	UV-Pharmaspec – 1700	DBK Instruments Ltd., Mumbai.

5.4 PREFORMULATION STUDIES

Preformulation may be described as a stage of development during which the physicochemical and biopharmaceutical properties of a drug substance are characterized. It is an important part of the drug development process. The information relating to drug development acquired during this phase is used for making critical decisions in subsequent stages of development. A wide variety of information must be generated to develop formulations rationally. Characterization of the drug is a very important step at the preformulation phase of product development followed by studying the properties of the excipients and their compatibility. (***E.F. Fiese ,1986***)

The API was tested for the following properties

- Organoleptic Properties
- Solubility
- Water Content
- Particle Size determination
- Flow Properties
    - Angle of Repose
    - Bulk Density
    - Tapped Density
    - Carr's Index
    - Hausner's Ratio
- Drug – Excipient compatibility study

5.4.1 Organoleptic Properties

The drug sample was viewed visually and viewed under the compound microscope for the determination of its color using the black and white backgrounds and nature of the drug sample. Then the results were compared with the official books.

5.4.2 Solubility

The solubility of the drug sample was carried out in different solvents (aqueous and organic) according to the United States Pharmacopoeia. The results are then compared with those given in the United States Pharmacopoeia.***(G. Bankeret.al,2000)***

5.4.3 Water Content

Methanol (35ml) was transferred to the titration vessel and titrated with Karl fisher reagent to the electrometric end point to consume any moisture that may be present. 300-500mg of API was transferred to the titration vessel and titrated with Karl fisher reagent to the electrometric endpoint. Water content present in the sample was calculated by the formulae: (***E.F. Fiese ,1986***)

Calculation:

$$\text{Water (\%)} = \frac{S \times F \times 100}{W}$$

Where,

S = Volume in ml of reagent consumed in the second titration

F = Water equivalent factor of KF reagent

W = Weight of sample taken in mg

5.4.4 Flow Properties

5.4.4.1 Angle of repose (θ)

It is a direct measure of flow property of powders. It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal.

Angle of repose was determined using funnel to pour the powder on the surface from a fixed height of 2cm. Circumference was drawn with a pencil on the graph paper and the radius of base of a pile was measured at 5 different points and average was taken for calculatingAngle of repose using following formula:

$$\text{Angle of Repose } (\Theta) = \tan^{-1}(h/r)$$

Where,

h = height of a pile (2 cm)

r = radius of pile base.

5.4.4.2 Bulk density

It is the ratio of given mass of powder and its bulk volume determined by measuring the volume of known mass of powder sample that has been passed through the screen in to graduating cylinder. (***E.F. Fiese ,1986***)

Bulk density was determined according to USP method I. The powder sample under test was screened through sieve no 18 and 10 gm of pure drug was accurately weighed and filled in a 100ml graduated cylinder and the powder was leveled and the unsettled volume (Vo) was noted. Bulk density (Db) was calculated in g/ml by the formula:

$$\mathbf{(Db) = M/Vo}$$

Where,

M = mass of powder taken

V_o= unsettled apparent volume

5.4.4.3 Tapped density

Tapped density was determined by USP method II. The powder sample under test was screened through sieve no.22 and 10 gm of pure drug was filled in 100ml graduated cylinder of tap density tester (electrolab, ETD 1020). The mechanical tapping of the cylinder was carried out using tapped density tester at a normal rate of 250 drops per minute for 500 times initially and the initial tapped volume (Va) was noted. Tapping was proceeded further for additional 750 times and volume was noted. The difference between two tapping volumes was calculated.

Tapping was continued for additional 250 tap if the difference is more than 2%. This was continued in increments of 250 taps until differences between volumes of subsequent tapping was less than 2%. This volume was noted as, the final tapped volume (Vo). The tapped density (Dt) was calculated in g/ml by the formula:

$$\mathbf{Dt = M/ Vo}$$

Where,

M= weight of sample powder

V_o = final tapped volume

\

5.4.4.4 Compressibility Index and Hausner Ratio

Compressibility index and hausner ratio are measures of the propensity of a powder to be compressed and provide relative importance of inter particulate interactions. The free flowing powder has less inter particulate interactions and bulk & tapped density difference is close when compared to poorer flowing materials. (***E.F. Fiese ,1986***)

Carr's index i.e., % compressibility indicates the flow property and packing ability of the tablet. It was determined by measuring both the bulk and tapped density of a powder. Compressibility Index was calculated using following equation:

$$\mathbf{CI\ (\%) = [(Dt-Db)/Dt]\ x100}$$

Where,

Dt = tapped density

Db = bulk density

Hausner's ratio was calculated using the formula:

$$\mathbf{Hausner\ Ratio = Dt/Db}$$

Where,

Dt = tapped density

Db = bulk density

5.4.5 Drug – Excipient Compatibility Study

Drug is in intimate contact with one or more excipient in all the dosage forms. Later it could affect the stability of drug. Knowledge of drug excipient interaction is useful in selecting an appropriate excipient.

API and excipients are taken in the ratios as mentioned in Table 10 and mixed together in a polybag for 5 min. Each sample mixture is divided into four parts (1gm each), transferred in to a glass vial and stored in different conditions as shown in Table 11.

All vials are properly sealed and loaded at respective conditions. The samples are checked for its description, related substance and water content by karlfisher.

TABLE: 10 DRUG AND EXCIPIENT RATIO FOR COMPATIBILITY STUDIES

S.No	Drug - Excipient	Ratio
1	Candesartan + Corn starch	1:5
2	Candesartan + PEG 6000	1:5
3	Candesartan + Calcium CMC	1:5
4	Candesartan + Klucel EF	1:5
5	Candesartan + Klucel LF	1:5
6	Candesartan + Ferric oxide red	1:0.1
7	Candesartan + Magnesium stearate	1:1
8	Candesartan + Avicel	1:5
9	Candesartan + Lactose	1:5

The prepared drug and excipient mixtures were evaluated at various intervals (As mentioned in Table 11) forphysical appearance, change in color and related substances by HPLC.

TABLE: 11 SAMPLING SCHEDULE

S.No	Condition	Duration	No. of Sets
1	Initial	0 days	1
2	$55^0C \pm 2^0C$	14 days	1
3	40 ± 2^0C & 75 ± 5% RH	14 days	1
4	40 ± 2^0C & 75 ± 5% RH	28 days	1

5.4.6 PREPARATION OF STANDARD CURVE

- Candesartan cilexetil (100 mg) was accurately weighed and dissolved in 100 ml of ethanol to give stock solution (1000 mcg/ml).

- Aliquots of 1000 mcg/ml solution were suitably diluted with methanol To give final concentrations of 5, 10, 15, 20 and 25 mcg/ml.

- The λ max was found by UV spectrum of Candesartan cilexetil in methanol, in the range of 200-400 nm, and it was found to be 255 nm.

- Absorbance was measured at 255 nm against methanol as a blank. Spectral characteristics of Candesartan cilexetil and linearity data are given in table.

TABLE:12 SPECTRAL CHARACTERISTICS OF CANDESARTAN CILEXETIL

Parameters	Value
λmax(nm)	255
Beer's law limits (mcg/ml) (c)	5-25
Molar absorptivity (lit/mol-1 cm-1)	2.0275304×10^{4}
Regression equation (Y*)	Y=0.03401x-0.00847
Slope (m)	3.4011×10^{-2}
Y - intercept (c)	8.4761×10^{-3}
Correlation coefficient (r2)	0.9998

TABLE:13 STANDARD CURVE OF CANDESARTAN CILEXETIL

Concentration(mcg/ml)	Absorbance
0	0.000
5	0.175
10	0.352
15	0.526
20	0.704
25	0.898

Figure no:18 UV spectrum of Candesartan cilexetil in methanol

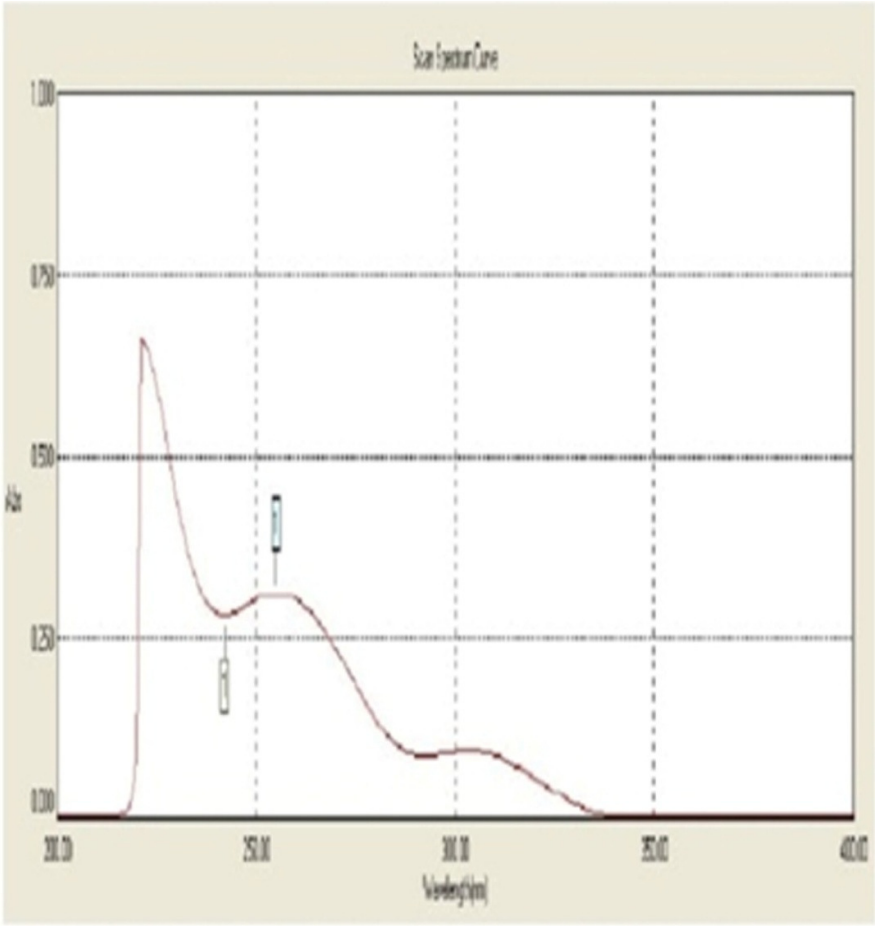
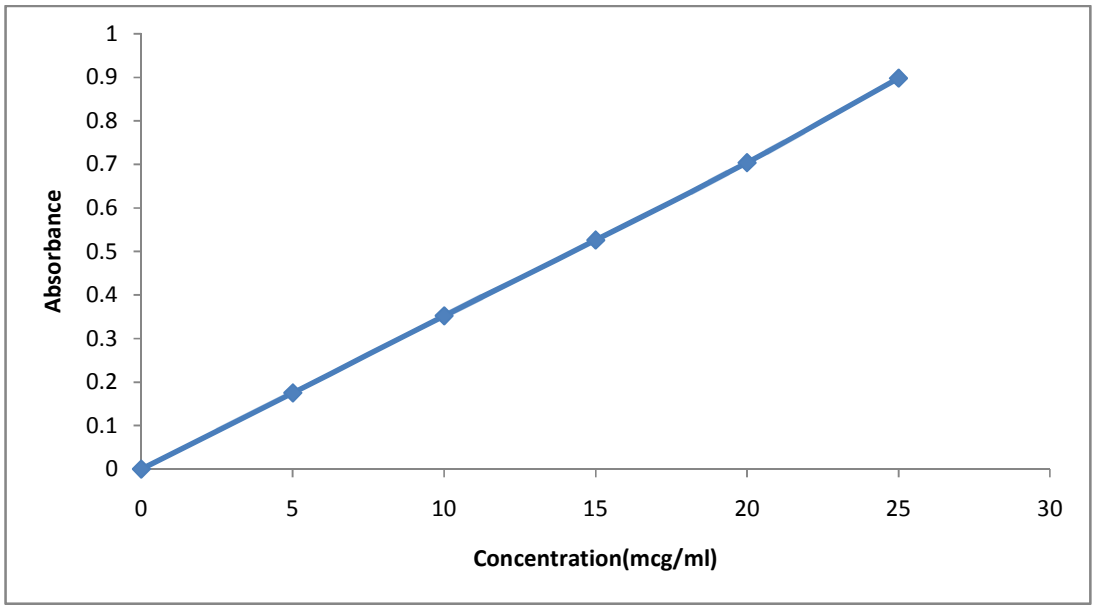


Figure no:19 Standard curve of Candesartan cilexetil



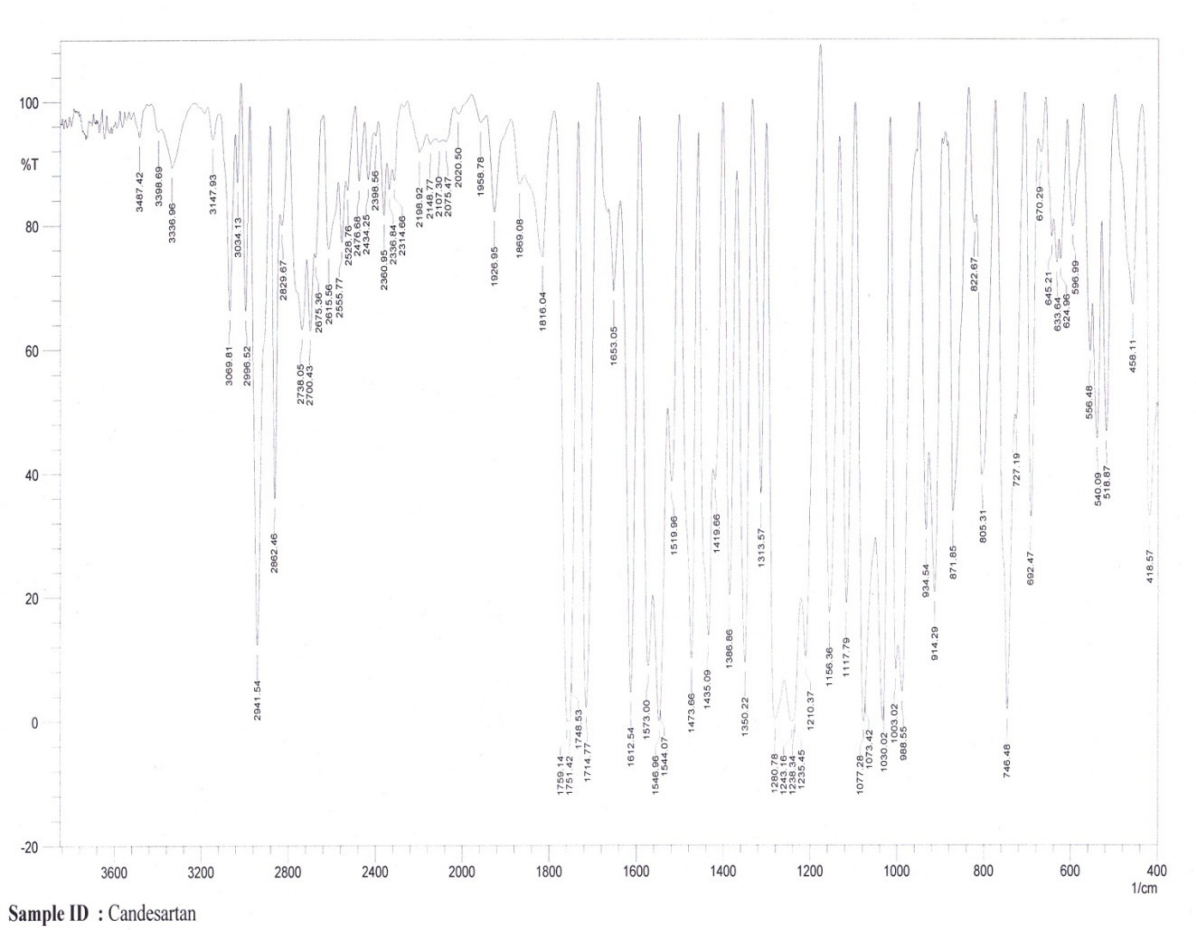
5.4.7 Identification of drug by FTIR

The identification of drug was done by FTIR Spectroscopy.

Method:

Triturate 1-2mg of the substance to be examined with 300-400 mg,unless otherwise specified, of finely powdered and dried potassium bromide R or potassium chloride R. These quantities are usually sufficient to give a disc of 10-15 mm diameter and a spectrum of suitable intensity.Infrared spectrophotometers are used for recording spectra in the region of 4000-650 cm^{-1}

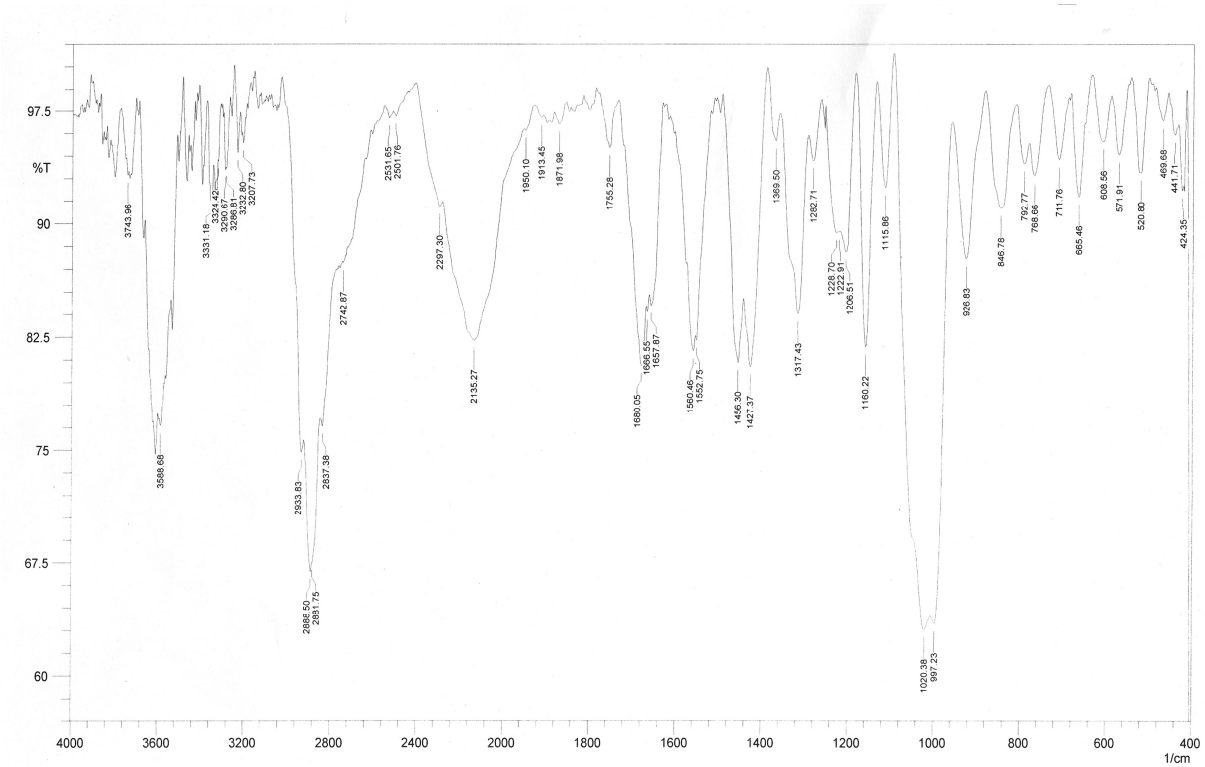
Figure no:20 FTIR spectrum of Candesartan cilexitil



IR REGION:

Functional group	Region range
N-H-Streching	3600-3200
C-H-Streching	2960-2850
C=O-Streching	1600-1450
C-N-Vibrations	1400-1040
C-O-Bending	900-650

Figure no:21 FTIR spectrum of candesrtan granules



Sample ID : Candesartan Granules

5.5 FORMULATION OF CANDESARTAN IR (32MG) TABLETS

5.5.1 Formulation Planning

The immediate release tablets containing 32mg candesartan cilexetil were prepared with a total tablet weight of 260mg.Based on the results of preformulation studies; to improve the flow properties, tablets were prepared by wet granulation technique and the composition is given in Table 14. Based on literature survey and compatibility tests excipients like microcrystalline cellulose (pH 101), poly ethylene glycol – 6000, pre gelatinized starch, hydroxypropylcellulose, carboxymethyl cellulose, magnesium stearate were used.

5.5.2 Manufacturing Procedure

- Weighed candesartan, lactose and pre gelatinized starchwas passed through 40 mesh and then mixed.
- Weighed poly ethylene glycol 6000 was transferred into 50ml of purified water and then stirred by using mechanical stirrer to get clear solution.
- Weighed klucel was poured in to above poly ethylene glycol solution and then stirred to get turbid solution by using mechanical stirrer.
- Above blend was made into dough mass by using binder solution.
- Dough mass was passed through 14 mesh to get wet granules and dried by using FBD at 60^{o}c.
- Dried granules were passed through 18 mesh.
- Weighed Cal.CMC and Mg.Stearate was passed through 40 mesh and then added to above granules and lubricated granules were compressed by rotary die press.

5.5.3 Compositions Formulations of Candesartan Cilexetil

The immediate release tablets of candesartan cilexetil 32mg has been formulated using the formula shown in the Table.

TABLE:14 COMPOSITIONS OF FORMULATIONS

Ingredients	**F-1**	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**	**F-7**	**F-8**	**F-9**	**F-10**
Candesartan	32	32	32	32	32	32	32	32	32	32
Lactose Mono Hydrate	155.98	155.98	164.97	164.97	166.97	145	52	52	-	164.97
PEG 6000	12	12	6	2	-	12	12	12	-	6
Lycatab PGS/ Corn starch	40	40	40	40	40	40	-	25	25	40
Ferric oxide Red	0.02	0.02	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Hydroxy propyl cellulose	8	8	8	12	12	10	12	12	12	8
PVP – K 30	-	-	-	-	-	7.8	-	-	-	-
Micro crystalline cellulose	-	-	-	-	-	-	125	100	150	-
Purified Water	70	70	70	70	70	70	70	70	120	70
Ca CMC	11.2	11.2	8	2	8	-	25	25	25	8
Mg.stearate	0.8	0.8	1.0	1	1	2.6	2	2	2	1.0
SLS	-	-	-	-	-	10	-	-	-	-
Total (mg)	**260**	**260**	**260**	**260**	**260**	**260**	**260**	**260**	**260**	**260**

6. EVALUATION STUDIES

6.1 Evaluation of granules

6.1.1 Flow Properties

6.1.1.1 Angle of repose (θ)

It is a direct measure of flow property of powders. It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal.

Angle of repose was determined using funnel to pour the powder on the surface from a fixed height of 2cm. Circumference was drawn with a pencil on the graph paper and the radius of base of a pile was measured at 5 different points and average was taken for calculatingAngle of repose using following formula

$$\textbf{Angle of Repose } (\Theta) = \text{Tan}^{-1} (h/r)$$

Where,

h = height of a pile (2 cm)

r = radius of pile base.

6.1.1.2 Bulk density

It is the ratio of given mass of powder and its bulk volume determined by measuring the volume of known mass of powder sample that has been passed through the screen in to graduating cylinder. ***(L.J. Ravin et.al,1990)***

Bulk density was determined according to USP method I. The powder sample under test was screened through sieve no 18 and 10 gm of pure drug was accurately weighed and filled in a 100ml graduated cylinder and the powder was leveled and the unsettled volume (Vo) was noted. Bulk density (Db) was calculated in g/ml by the formula:

$$\textbf{(Db)= M/Vo}$$

Where,

M = mass of powder taken

V_o= unsettled apparent volume

6.1.1.3 Tapped density

Tapped density was determined by USP method II. The powder sample under test was screened through sieve no.22 and 10 gm of pure drug was filled in 100ml graduated cylinder of tap density tester (electrolab, ETD 1020). The mechanical tapping of the cylinder was carried out using tapped density tester at a normal rate of 250 drops per minute for 500 times initially and the initial tapped volume (Va) was noted. Tapping was proceeded further for additional 750 times and volume was noted. The difference between two tapping volumes was calculated. ***(L.J. Ravin et.al,1990)***

Tapping was continued for additional 250 tap if the difference is more than 2%. This was continued in increments of 250 taps until differences between volumes of subsequent tapping was less than 2%. This volume was noted as, the final tapped volume (Vo). The tapped density (Dt) was calculated in g/ml by the formula:

$$\mathbf{Dt = M/ Vo}$$

Where,

M= weight of sample powder

V_o = final tapped volume

6.1.1.4 Compressibility Index and Hausner Ratio

Compressibility index and hausner ratio are measures of the propensity of a powder to be compressed and provide relative importance of inter particulate interactions. The free flowing powder has less inter particulate interactions and bulk & tapped density difference is close when compared to poorer flowing materials.

Carr's index i.e., % compressibility indicates the flow property and packing ability of the tablet. It was determined by measuring both the bulk and tapped density of a powder. Compressibility Index was calculated using following equation

$$\mathbf{CI\ (\%) = [(Dt\text{-}Db)/Dt]\ x100}$$

Where,

Dt = tapped density

Db = bulk density

Hausner's ratio was calculated using the formula:

Hausner Ratio = Dt/Db

Where,

Dt = tapped density

Db = bulk density

6.2 Evaluation of tablets

6.2.1 Weight variation

Weight variation was calculated as per method descried in USP. Twenty tablets were selected at random and their average weight was determined using an electronic balance. The tablets were weighed individually and compared with average weight.*(**Seitz, J. A. et.al, 1965)***

6.2.2 Tablet thickness and Hardness

Thickness was measured using venier caliper and hardness of formulations were measured using a Hardness Tester. Ten tablets of each trial formulation were taken and measured individually at frequent intervals.

6.3.3 Friability (%)

Friability was determined by taking 20 tablets. Tablets samples were weighed accurately and placed in friabilator after the given specification (4 min at 25 rpm). The tablets were weighed again and % friability was then calculated by:

$$\%F = \{(W - W_0)/W\} \times 100$$

Where,

% F = Friability of tablets in percent.

W = Initial Wight of tablets.

W_O = Final weight of tablets.

6.3.4 Disintegration Test

Disintegration test was measured using USP tablet disintegration test apparatus (ED2AL, Electrolab, India) by using 900 ml of distilled water at room temperature (37±20C). ***(Odeku et.al,2003)***

6.3.5 Assay (HPLC)

6.3.5.1 Chromatographic conditions

Column	:	Hypersill BDS-C8 (150 X 4.6mm) 5µm
Flow rate	:	1.5ml/min
Wave length	:	UV-210nm
Injection volume	:	10µL
Column temperature	:	40^{o}C
Run time	:	25min

Blank, standard and sample preparations of equal volume were separately injected and the chromatograms are recorded. The content (%) of candesartan in the portion of candesartan tablet was calculated by the formula: ***(Odeku et.al,2003)***

6.3.5.2 Calculation

% of content of candesartan cilexetil

$$\frac{TA}{SA} \times \frac{SW}{100} \times \frac{5}{50} \times \frac{100}{TW} \times \frac{100X}{2} \times \frac{P}{100} X \frac{AvgWt}{LA} \times 100$$

Where,

SA	=	Peak area response due of candesartan from standard preparation
TA	=	Peak area response due of candesartan from sample preparation
SW	=	Weight of candesartan working standard (mg)
P	=	Purity of candesartan working standard
TW	=	Weight of sample
LA	=	Label amount

6.3.6 *In-vitro* Dissolution Release study

6.3.6.1 Dissolution conditions

Medium	:	0.7% tween-20 in 0.05 M phosphate buffer, PH 6.5
Volume	:	900ml
Temperature	:	$37^{o}C \pm 0.5^{o}C$
Apparatus	:	USP type –II (paddle)
RPM	:	50
Time interval	:	10, 20, 30, 45 and 60 min.

Blank, standard and sample preparations of equal volume were separately injected and the chromatograms are recorded. The content (%) of candesartan in the portion of candesartan tablet was calculated by the formula

% of labeled amount of candesartan dissolved:

$$\frac{TA}{SA} \times \frac{SW}{200} \times \frac{5}{25} \times \frac{900}{1} \times \frac{P}{100} \times \frac{100}{32}$$

Where,

SA	=	Peak area response due of candesartan from standard preparation
TA	=	Peak area response due of candesartan from sample preparation
SW	=	Weight of candesartan working standard (mg)
P	=	Purity of candesartan working standard

7. STABILITY STUDIES

Dissolution of trial F – 08 tablets were comparable with reference product. So tablets of this batch were kept for stability studies. The tablets were tested for average weight, thickness, hardness, friability, disintegration, assay, water content and related substance at initial, 1 month and 3 months.

The results of stability studies are shown in Table. After 3 months the physical parameters of the tablets were same. Drug content, water content and related substance are with inthe limits.

TABLE:15 STABILITY STUDY DATA OF FORMULATION F – 08

S.No	Parameters	Conditions			
		Initial	**$25^0C \pm 2^0C$**	**40 ± 2^0C & 75 ± 5% RH**	
		0 Day	**3 Months**	**1 Month**	**3 Month**
1	Average Weight (mg)	260.2 ± 0.13	259.9± 0.2	260.4± 0.23	260.6± 0.3
2	Thickness (cm)	3.53 ± 0.02	3.52 ± 0.04	3.52 ± 0.06	3.50 ± 0.02
3	Hardness (kg/cm^2)	8.12 ± 0.47	8.11± 0.24	8.1± 0.36	7.9± 0.45
4	Friability (%)	0.06	0.07	0.17	0.19
5	Disintegration (min)	11	10	11	9
6	Assay (%)	99.8	99.9	98.7	98.6
7	Water content (%)	4.6	4.5	4.3	4.5

TABLE:16 DISSOLUTION PROFILE OF FORMULATION F – 08 STABILITY STUDY

S.No	Time(min)	Conditions			
		Initial	$25^0C \pm 2^0C$	40 ± 2^0C & 75 ± 5% RH	
		0 Day	3 Months	1 Month	3 Months
1	10	67.4	65.8	66.9	64.3
2	20	94.5	93.6	94.1	93.1
3	30	98.9	97.4	98.6	97.6
4	45	99.7	98.8	99.6	98.8
5	60	99.9	99.3	99.8	99.6

Figure No:22 Dissolution profile for initial and 3 months stability study of formulation F-8 at $25^0c \pm 2^0c$

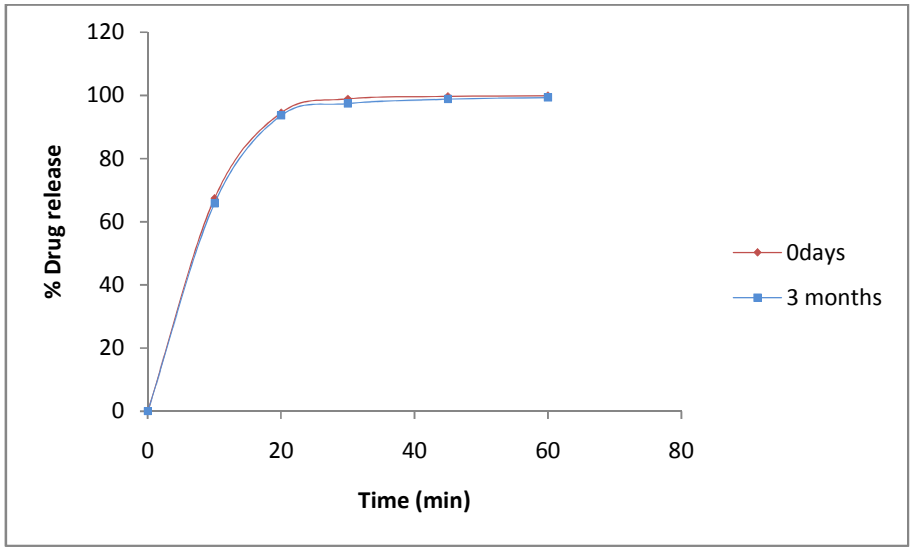
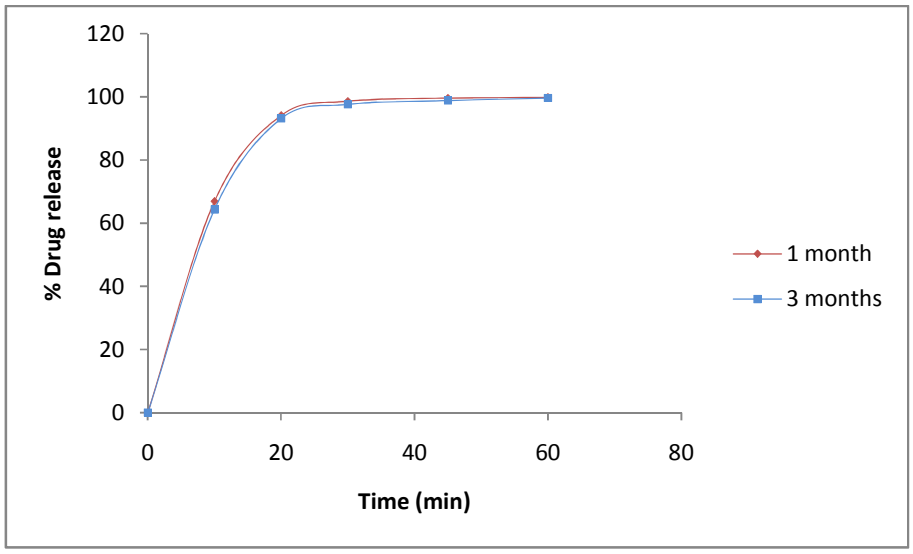


Figure No:23 Dissolution profile for 1 month and 3 months stability study of formulation F-8 at 40 ± 2^0C & 75 ± 5% RH



8. RESULTS AND DISCUSSIONS

8.1 Preformulation studies

Preformulation studies like physical characterization, solubility, moisture content, flow properties like angle of repose, bulk density, tapped density, compressibility index and hausner ratio were performed for drug and the obtained data are presented in the Table.

TABLE:17 PHYSICAL CHARACTERIZATION OF CANDESARTAN CILEXETIL

S.No:	Description	Result
1.	Appearance	White to off-white powder
2.	Odour	Characteristic odour.
3.	Solubility	Freely soluble in Methylene chloride. Slightly soluble in methanol, Practically insoluble in water.
4.	Water Content	0.07 %

TABLE:18 FLOW PROPERTIES OF API

S.No	Flow Properties	Result
1	Bulk density (g/ml)	0.264
2	Tapped density (g/ml)	0.562
3	Carr's index (%)	52.94%
4	Hausner's ratio	2.12
5	Angle of repose	22.8 ^{o}

The results of the study showed that physical characterization of Candesartan cilexetil (API) complies with the USP specifications and API was found to have poor flow property.

8.1.3 COMPATIBILITY STUDY

The compatibility study for Candesartan cilexetil - excipients mixture was carried out to quantify the related substance and physical appearance.

No Characteristic change in the color of the mixture was observed and no additional degradation of the product was observed. The increase in impurities at the end of the accelerated condition is not significant. All the excipients are stable and compatible with active ingredient. Hence, it is recommended that the above excipients can be used in further formulation development trials.

TABLE:19 COMPATIBILITY STUDY

EXCEPIENT	DESCRIPTION	
	DRUG:EXCEPIENT(1:1) $55^0C\pm2^{0C}$	**DRUG:EXCEPIENT(1:1) $45^0C\pm2^0C$&75±5% RH**
Lactose	White to off White Powder	White to off White Powder
PEG 6000	White Flaky Powder	White Flaky Powder
PG Starch	White to off White Powder	White to off White Powder
HPC	White to off White Powder	White to off White Powder
Ca CMC	White to off White Powder	White to off White Powder
Mg.Stearate	White to off White Powder	White to off White Powder

8.2 RESULTS OF FLOW PROPERTIES OF LUBRICATED BLEND

The evaluation results for flow properties of granules are described in the following Table.

TABLE:20 EVALUATIONS OF GRANULES

S.No	Formulations	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility Index (%)	Hausner's Ratio
1	F-1	0.596	0.785	24.07	1.31
2	F-2	0.581	0.714	18.60	1.22
3	F-3	0.654	0.802	18.45	1.22
4	F-4	0.694	0.834	16.67	1.2
5	F-5	0.480	0.625	23.07	1.30
6	F-6	0.519	0.732	29.09	1.443
7	F-7	0.583	0.745	21.74	1.277
8	F-8	0.348	0.527	33.96	1.514
9	F-9	0.510	0.641	20.40	1.25
10	F-10	0.500	0.735	32	1.470

INFERENCE:

The formulation trialsF–1, F–5, F–7,F-9 showed "passable" flow propertieswhere as trials F-2, F-3, F-4, F-8, showed "fair" flow properties and trials F-6, F–10 showed very poor flow properties.

8.3 RESULTS OF EVALUATION OF TABLETS

The evaluation results of in process properties of tablets are described in the following Table.

TABLE:21 EVALUATION OF TABLETS

S.No	Formulations	Thickness (mm)	Hardness (kg/cm^2)	Disintegration (Min)	Friability (%)	Assay (%)
1	F-1	3.62 ± 0.099	4.1 ± 0.31	3.16	0.153	96.4
2	F-2	3.62 ± 0.016	5.1 ± 0.42	3.02	0.106	97.3
3	F-3	3.46 ± 0.035	6.19 ± 0.22	8.5	0.377	94.1
4	F-4	3.46 ± 0.024	9.75 ± 0.51	14.55	0.24	98.5
5	F-5	3.48 ± 0.029	10.44 ± 0.49	11.5	0.17	97.4
6	F-6	3.47 ± 0.053	5.46 ± 0.32	11.2	0.28	98.3
7	F-7	3.47 ± 0.052	9.45 ± 0.59	12	0.23	92.4
8	F-8	3.53 ± 0.022	8.12 ± 0.47	11	0.06	99.8
9	F-9	3.55 ± 0.019	9.6 ± 0.35	5.5	0.06	98.5
10	F-10	3.55 ± 0.016	7.1 ± 0.27	2	0.167	98.2
11	Innovator	3.50 ± 0.04	9.8 ± 0.14	11.17	0.15	98.8

INFERENCE:

Formulation trials F-1, F-2, F-6 did not achieve required hardness;drug content was found to be less in trial F-7, Trials F-8, F-9 achieved required hardness, friability and thickness.

8.4 *IN-VITRO* DISSOLUTION RELEASE

Comparative *In-vitro* dissolution release profile for reference drug and all formulations at 60 minutes is given in the Table.

TABLE:22 PERCENTAGE OF RELEASE

S.No	Time	% of Drug Release										
		F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	Innovator
1	10	65.6	71.5	69.1	28.0	58.9	39.3	36.3	66.9	75.3	80.4	41.2
2	20	71.8	78.7	89.0	52.6	81.6	69.2	69.7	94.3	83.6	84.4	75.6
3	30	79.3	83.5	96.6	81.1	93.4	89.4	83.9	98.7	87.4	90.7	90.4
4	45	86.1	91.4	97.8	91.7	95.1	93.3	91.6	99.3	92.8	92.4	96.7
5	60	93.4	96.8	98.4	98.8	97.8	96.6	96.5	99.9	98.9	94.9	98.7

We selected **F - 8** as the best formulation as it showed total drug release with in 30 min than all other formulations when compared to the reference product as well as showed greater drug release at all the tested time points compared to the innovator product.

Figure No:24 *In-vitro* Drug release of formulation F – 1.

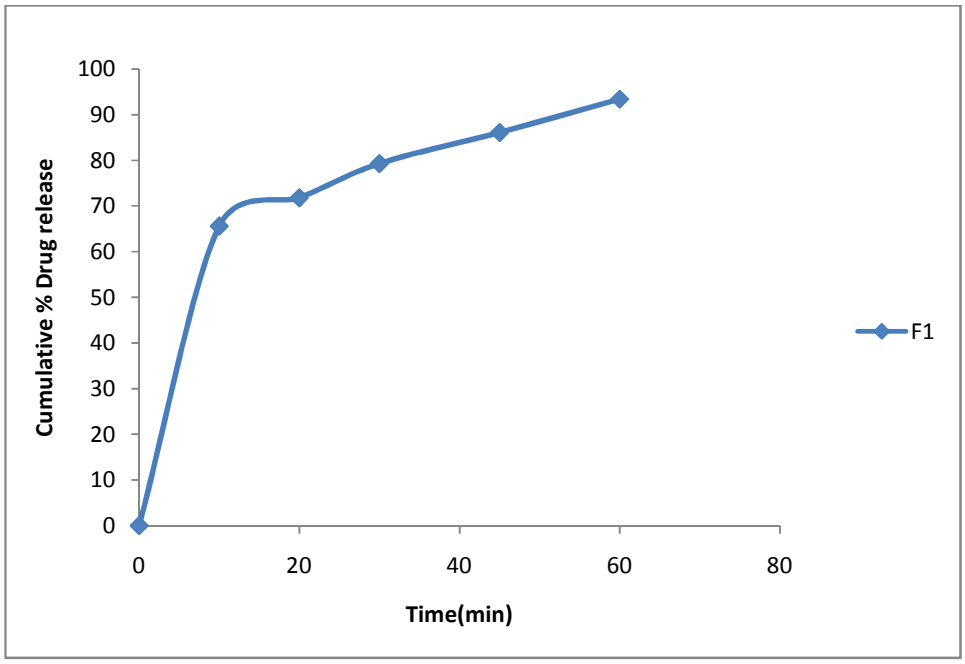


Figure No:25 *In-vitro* Drug release of formulation F – 2.

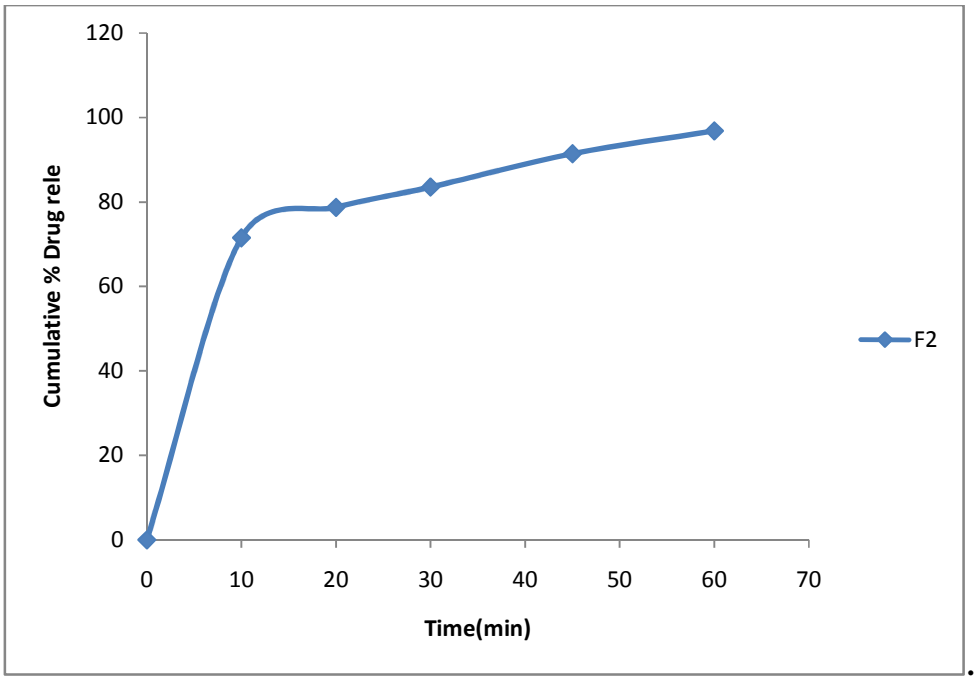


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Figure No:26 *In-vitro* Drug release of formulation F – 3.

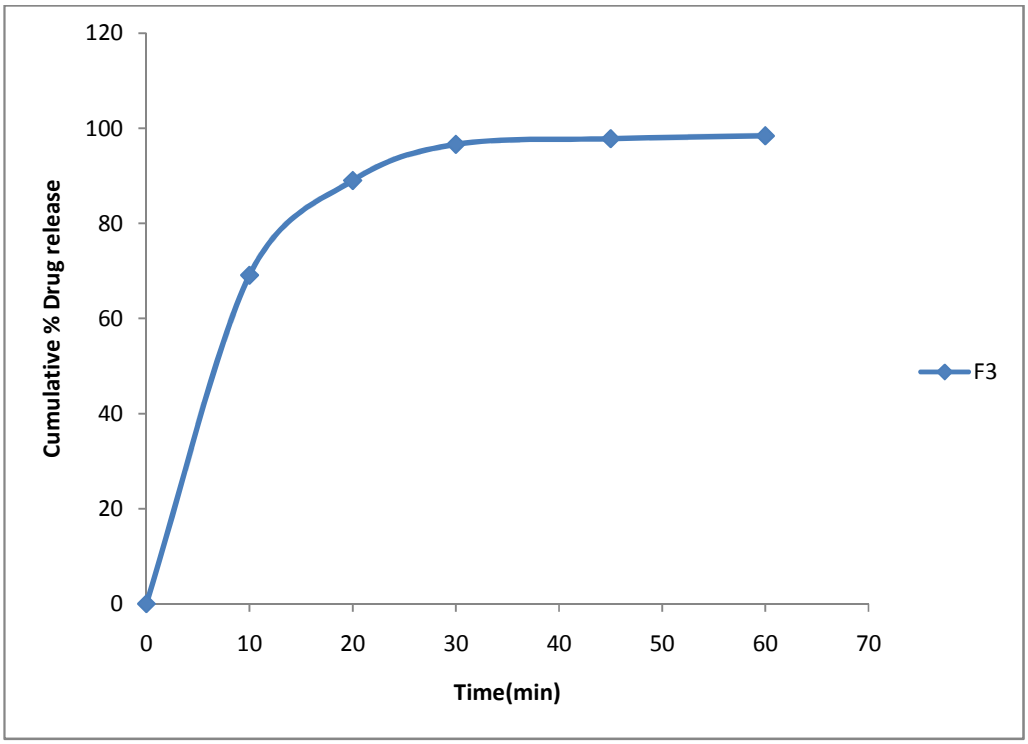


Figure No:27 *In-vitro* Drug release of formulation F – 4.

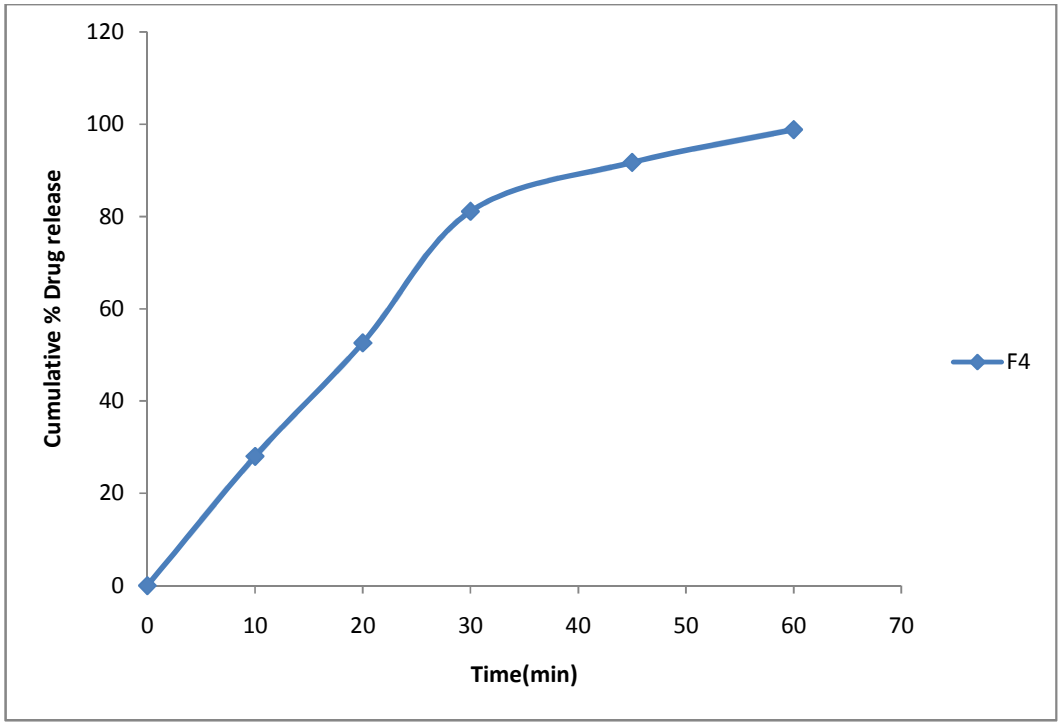


Figure No:28 *In-vitro* Drug release of formulation F – 5

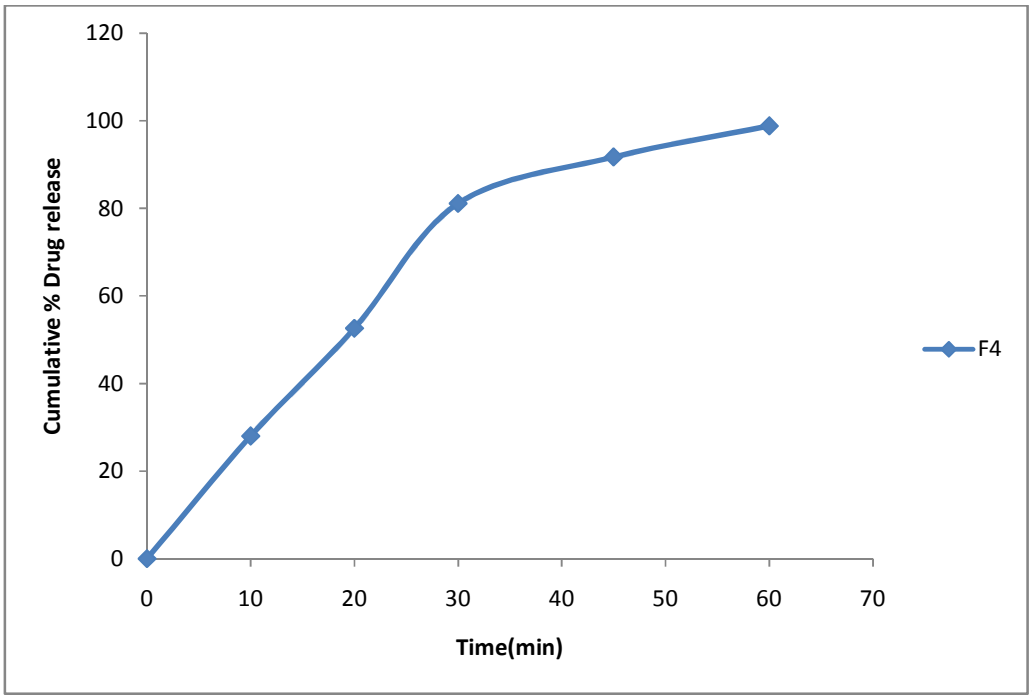


Figure No:29 *In-vitro* Drug release of formulation F – 6.

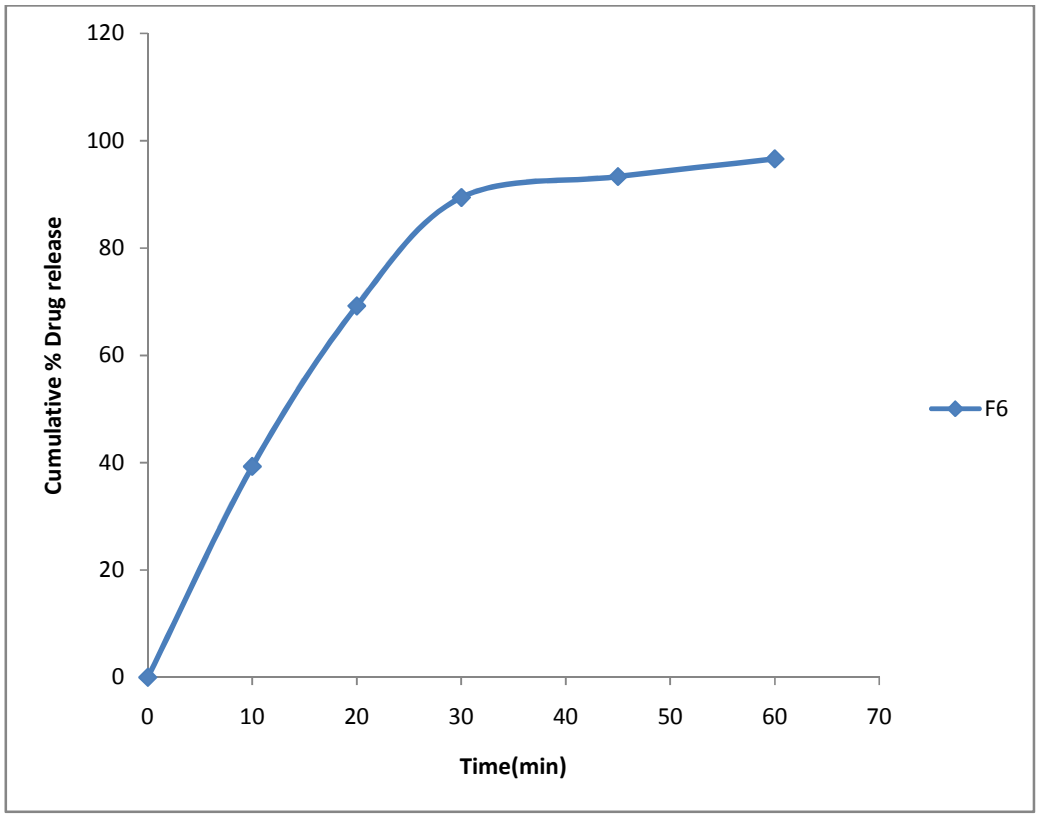


Figure No:30 *In-vitro* Drug release of formulation F – 7.

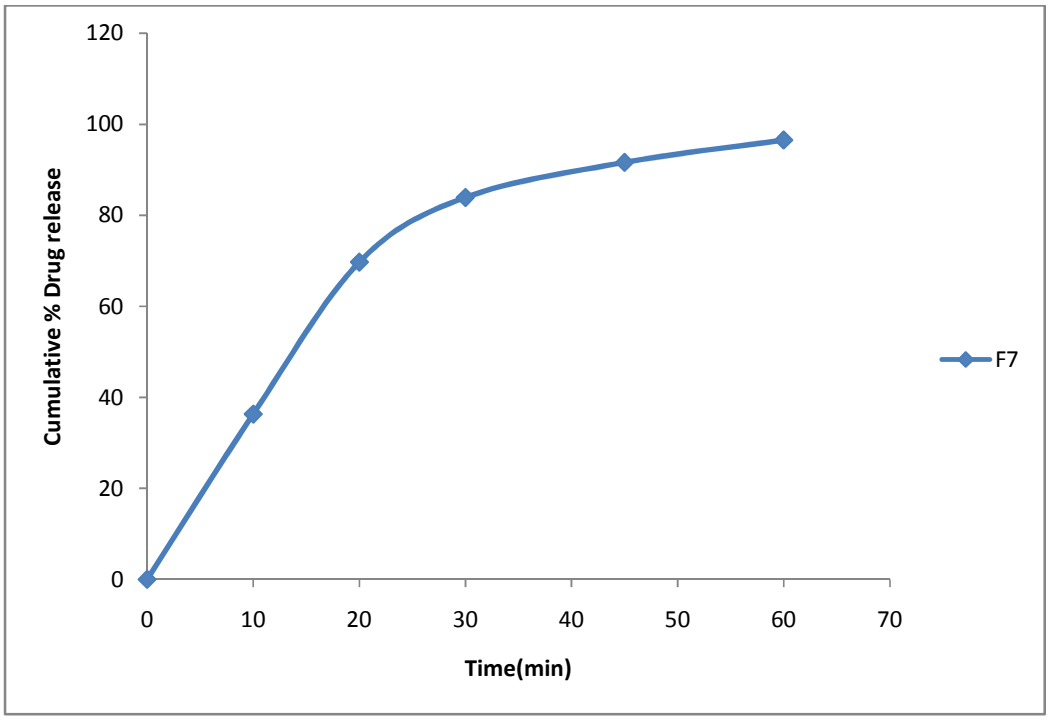


Figure No:31 *In-vitro* Drug release of formulation F – 8.

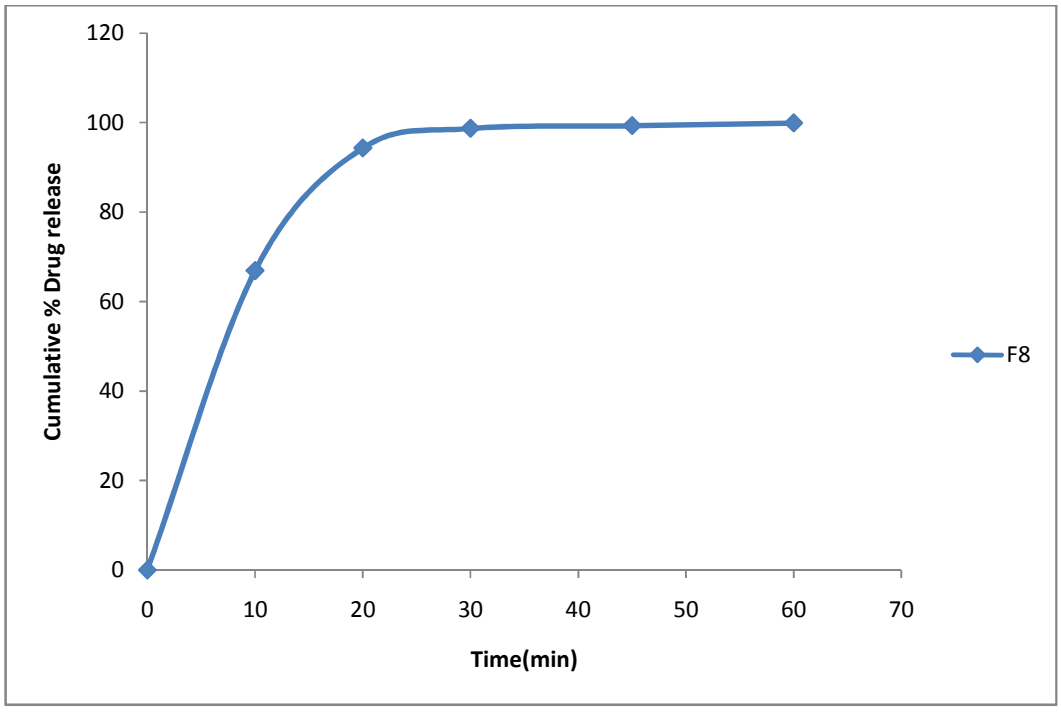


Figure No:32 *In-vitro* Drug release of formulation F – 9.

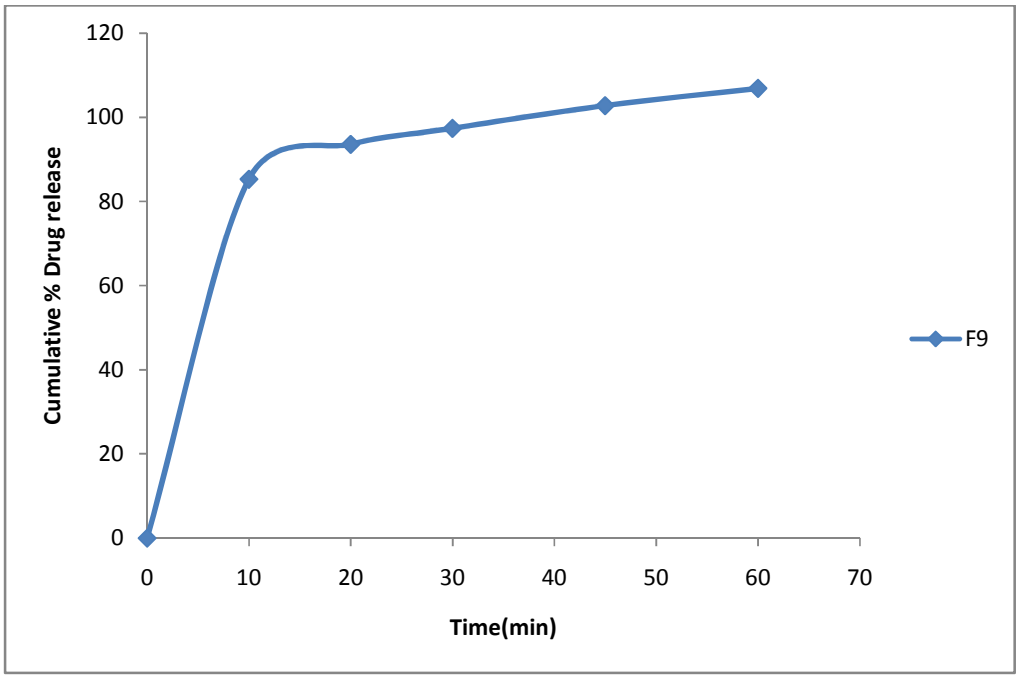


Figure No:33 *In-vitro* Drug release of formulation F – 10

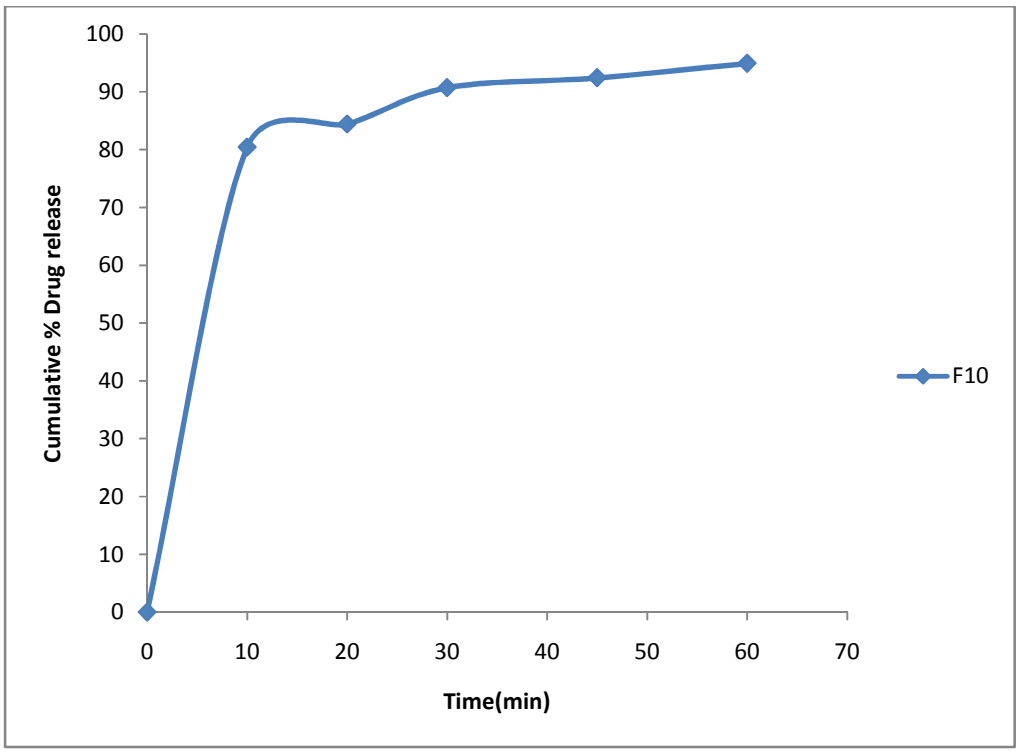


Figure No:34 *In-vitro* Drug release of Reference sample.

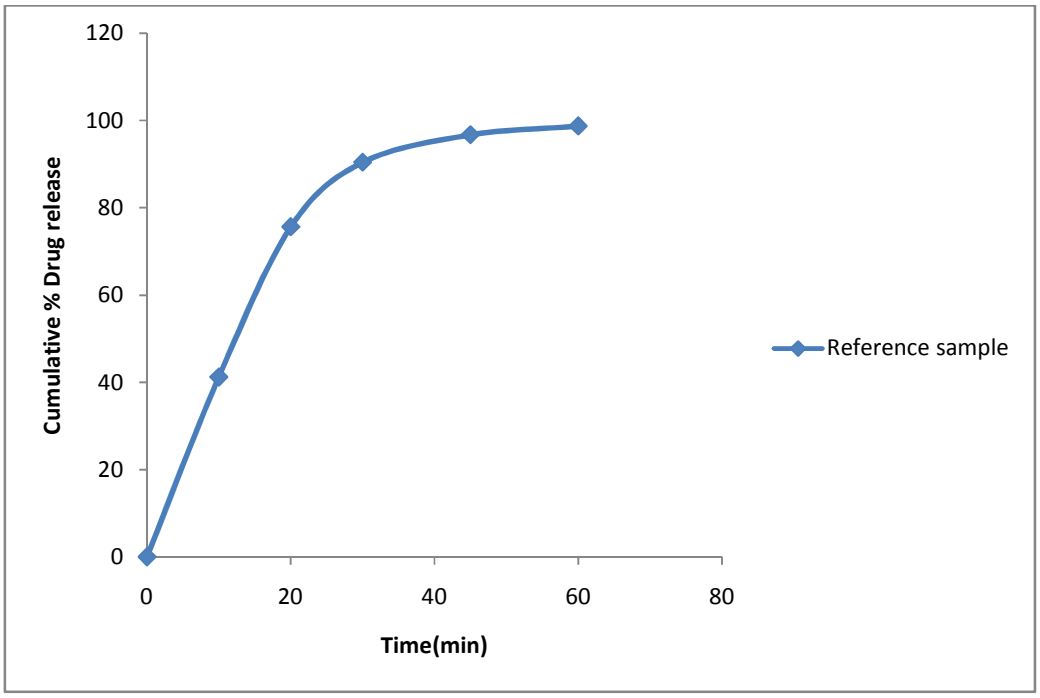


Figure No:35 Comparative *In-vitro* Drug release of Formulations F – 1, 2, 3,4,5 and reference sample.

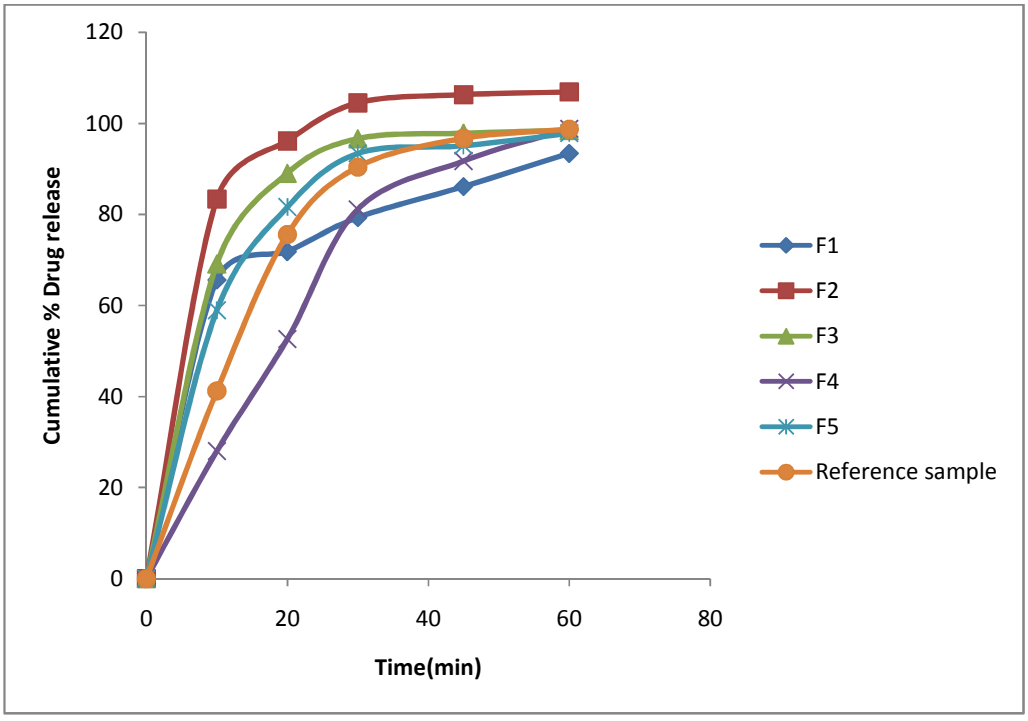


Figure No:36 Comparative *In-vitro* Drug release of Formulations F – 6,7,8,9,10 and reference sample.

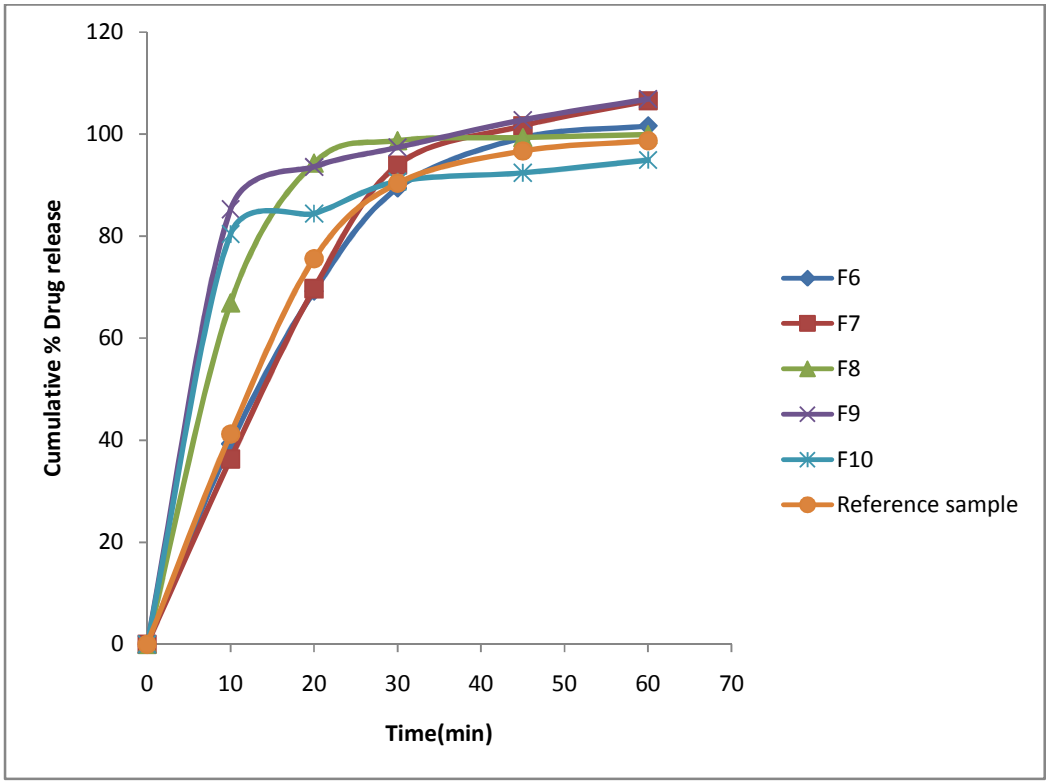
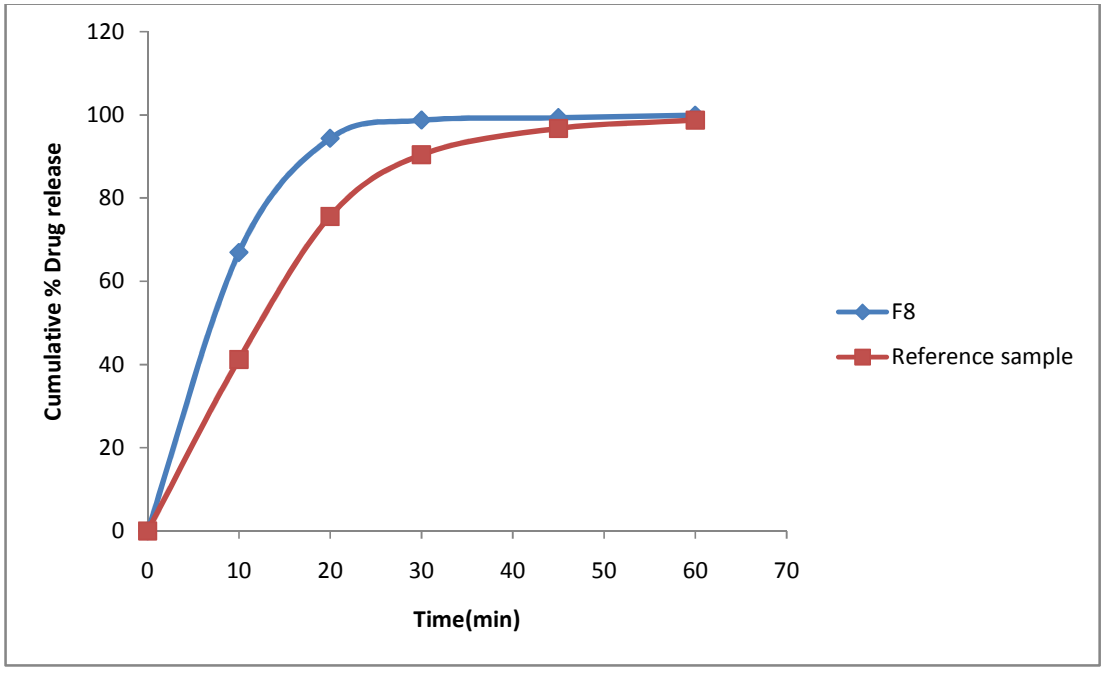


Figure No:37 Comparative *In-vitro* Drug release of Formulation F – 8 and reference sample.



DISCUSSION

Formulations F– 1 & 2 of Candesartan cilexetil (32mg) was formulated by using unmicronized and micronized API. This formulation was done to determine whether particle size vary with flow properties or not. The results of the study showed that micronized API (F – 2) has good flow properties. Hence micronized API was selected for further studies.

Formulation F – 3In this study candesartan cilexetil was formulated by reducing PEG and Ca.CMC concentration. This study was done to match the reference drug in terms of appearance, thickness, hardness and in-vitro drug release. The results showed that the total drug release was found to be less when compared to the reference product.

Formulation F – 4 **of** Candesartan cilexetil was formulated by reducing the quantity of PEG and increasing the amount of Klucel. The results showed that the total drug release was found to be less when compared to the reference product.

Formulation F-5 was formulated without PEG. The results of this study showed poor flow properties.

Formulation F-6 of Candesartan cilexetil was formulated by including Povidone k-30 as binder**.** The results of this study showed very poor flow properties.

Formulation F-7 of Candesartan cilexetil was formulated by incorporating Avicel PH 101 and eliminating Corn starch. The results showed passable flow properties and did not achieve required assay value.

Formulation F-8 of Candesartan cilexetil was formulated by incorporating Avicel PH 101 and reducing the quantity of Lactose and Starch. The results showed fair flow properties and achieved total drug release with in 30min.

Formulation F-9 was formulated by incorporating Avicel PH 101 and eliminating Lactose, PEG. The formulation achieved required drug release but showed passable flow properties

Formulation F-10 was formulated using direct compression method. Spray dried lactose was used instead of lactose. The study resulted in poor flow properties.

9. SUMMARY AND CONCLUSION

The present study was to develope and evaluate candesartan cilexetil tablets (32 mg).

Based on literature survey and compatibility test excipients like microcrystalline cellulose (pH 101), PEG – 6000, pre gelatinized starch, hydroxypropyl cellulose, carboxy methyl cellulose, magnesium stearate were used. In this present study, the tablets were prepared by using wet granulation technique. In order to optimize the product, different formulations were developed.

All the formulations were evaluated for physical characteristics, disintegration, *in-vitro*dissolution and stability studies.

Based on the dissolution profile and physical characteristics Formulation F – 08 was selected as the best formulation for further studies.

Stability studies were performed for this batch for 1 and 3 months under accelerated and long term testing conditions. The product was analyzed for physical appearance, hardness, thickness, friability, loss on drying, disintegration, assay and related substance at different time intervals. The results obtained were found to be with in the specified limits.

The confirmatory batch is under 6 months accelerated stability condition, based on the result, a pilot scale will be executed.

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